Evidence for the use of high flow nasal cannula therapy for respiratory management in paediatric units

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School of Nursing, Midwifery And Social Work
Abstract

Introduction

High flow nasal cannula (HFNC) oxygen therapy is a non-invasive form of respiratory support that is rapidly being taken up in paediatric intensive care units (PICU). For infants with bronchiolitis – who are the largest non-elective source of admissions to a PICU – there is some evidence that using HFNC therapy reduces the need for intubation and mechanical ventilation. The aim of this thesis is to explore, describe, critique and add to the evidence surrounding the use of HFNC therapy in the paediatric population for the management of respiratory distress.

Methodology

A case series analysis was undertaken to describe common pathophysiology presentations to a PICU that used HFNC therapy as a method of respiratory treatment. Consent was sought from individual patients who represented common presentations of patients requiring respiratory support in a PICU (asthma, bronchiolitis and cardiomyopathy).

A Cochrane systematic review was undertaken to determine the evidence for the clinical application of HFNC in the paediatric population. However, there remains a paucity of literature on HFNC application in lower acuity settings.

To address this, a pilot study was undertaken in the Paediatric Emergency Department (PED) of the Mater Children's Hospital (MCH), Brisbane, Australia, with infants with bronchiolitis who met the inclusion criteria and for whom parental consent was obtained. Once enrolled, HFNC therapy was commenced, and observations recorded at least hourly until treatment cessation. A comparison group was identified and included during the course of the study, consisting of all infants who were eligible but not enrolled during the study period. The study protocol detailed the clinical treatment of those infants in the trial group, and no other changes were made to the usual management of infants with bronchiolitis during the study period. The primary outcome of interest was PICU admission. Secondary outcomes included: physiological response to HFNC; adverse outcomes; intubation rates; and hospital and PICU length of stay.
**Results**

The case series analysis conducted indicated that HFNC therapy was successful in managing three patients with differing underlying pathophysiologies that caused respiratory distress.

The Cochrane systematic review did not identify any studies that matched its inclusion criteria.

Sixty-one infants were enrolled in the pilot study and 33 who met the inclusion criteria were later identified and formed the comparison group. Infants managed with HFNC therapy were four times less likely to require admission to PICU compared to those infants managed with standard low flow nasal oxygen therapy (OR 4.086, p=0.043). No infant, in either group, required intubation or mechanical ventilation. However, not all infants responded to HFNC therapy. Heart rate, respiratory rate and HiFOD score (a composite of physiological scores) indicated response to treatment over time (Generalised Linear Model p<0.001). The HFNC group successfully managed on the ward (Responders) had a mean reduction in heart rate of 13 bpm within 60 minutes of HFNC commencing. Whereas the heart rate of the HFNC group who were admitted to PICU (Non-Responders) increased (p=0.02). Likewise HiFOD scores also significantly reduced in the HFNC Responders with Non-Responders maintaining or slightly decreasing their HiFOD score (p=0.006) at 60 minutes. A similar trend was observed with respiratory rate; however this did not become significant until 180 minutes (p=0.001).

**Discussion**

Clinical uptake of HFNC in the intensive care setting is increasing. Intensive care settings are increasingly using HFNC therapy with reported clinical effect. However, the literature contains a paucity of evidence about its appropriate use and effectiveness, with only one small paediatric RCT conducted to date. The case series analysis revealed that using HFNC therapy may be safe and effective in the clinical management of infants with respiratory impairment. Further, the results of the pilot study indicate that HFNC therapy in low acuity settings, implemented as per the developed protocol, may reduce PICU admissions for infants with bronchiolitis. Additionally, the clinical reduction in heart rate and HiFOD scores at 60 minutes suggests that individual infants who receive HFNC therapy in a low acuity environment, but who do not respond within this time, may need to have their treatment reviewed and intervention escalated. These findings have implications for the effective management of bronchiolitis globally.
Conclusion

Bronchiolitis is the largest cause of PICU admissions. This thesis examines the evidence and builds on the extant literature by reporting a case series, a systematic review and a pilot study. Based on the results of this thesis, a trial of HFNC therapy in a low acuity setting may be considered, with anticipated clinical improvement evident in 60 minutes. This may indicate that the patient can be managed outside of an intensive care setting. Preventing PICU admissions will likely reduce both financial and social impact on hospitals and families.
Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications during candidature

Peer-reviewed publications


Conference abstracts


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Publications included in this thesis

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None.
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Keywords

Bronchiolitis, infants, paediatric ward, high flow nasal cannula, oxygen therapy

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List of Abbreviations

ALRI  Acute lower respiratory infection
ANOVA Analysis of variance
ARF Acute respiratory failure
AUROC Area under the curve receiver operator characteristics
CARG Cochrane Anaesthesia Review Group
CEWT Children's Early Warning Tool
CI Confidence interval
CNE Clinical Nurse Educator
CNRG Cochrane Neonatal Review Group
CPAP Continuous positive airway pressure
DMSC Data monitoring and safety committee
GLM Generalised linear model
HFNC High flow nasal cannula
HHHFNC Heated humidified high flow nasal cannula
HiFOD High Flow Oxygen Data
HREC Human and Research Ethics Committee
ICU Intensive care unit
LOS Length of stay
MCH Mater Children's Hospital
MEC Mater Education Centre
MET Medical emergency teams
NICU Neonatal intensive care unit
NIV Non-invasive ventilation
NP Nasopharyngeal pressure
PAP Positive airway pressure
PED Paediatric emergency department
PEWSS Pediatric Early Warning System Score
PEWT Paediatric Early Warning Tool
PICU Paediatric intensive care unit
RCT Randomised controlled trial
RDAI Respiratory Distress Assessment Instrument
RIP Respiratory inductive plethysmography
ROC Receiver operator characteristic
RSV Respiratory syncytial virus
VILI Ventilator induced lung injury
ARF Acute respiratory failure
COPD Chronic obstructive pulmonary disease
ED Emergency department
EELI End expiratory lung impedance
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<td>HDU</td>
<td>High dependency unit</td>
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<tr>
<td>HFTTO</td>
<td>High flow trans tracheal oxygenation</td>
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<td>HMPV</td>
<td>Human metapneuma virus</td>
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<td>LFNC</td>
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<td>NC</td>
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<td>NCPAP</td>
<td>Nasal continuous positive airway pressure</td>
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<td>NG</td>
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<td>NRB</td>
<td>Non-rebreather</td>
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<td>PEWS</td>
<td>Pediatric early warning system</td>
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<td>Pediatric Risk of Mortality score</td>
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<td>RDS</td>
<td>Respiratory distress syndrome</td>
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<td>RR</td>
<td>Respiratory rate</td>
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<tr>
<td>TREND</td>
<td>Transparent reporting of evaluations with nonrandomised designs</td>
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<td>WOB</td>
<td>Work of breathing</td>
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Chapter 1: Introduction

The most frequent reason that children less than two years of age are admitted to hospital is due to viral lower respiratory tract infections, the most common of which is bronchiolitis. Bronchiolitis is characterised by an acute inflammatory response in the small airways of the lower respiratory tract, with common symptoms including fever, cough, expiratory wheeze, bronchospasm, and rhinitis. The treatment has remained unchanged since the 1950s and 60s and incorporates oxygen therapy and fluid management. Infants with bronchiolitis can, however, still develop symptoms of respiratory distress. It is estimated that 10–15% of infants admitted to hospital with bronchiolitis will go on to require intensive care for their worsening respiratory state.

Of those admitted to an Intensive Care Unit (ICU), 9% will require mechanical ventilation. Mechanical ventilation can damage the lungs further, and this ventilator induced lung injury (VILI), may lead to chronic lung disease. Finding other conservative methods of supporting the respiratory system, without resorting to invasive means such as intubation and mechanical ventilation, is therefore important.

Non-invasive ventilation in the form of continuous positive airway pressure (CPAP) has become an increasingly popular modality to prevent invasive mechanical ventilation and its associated risks. CPAP can be delivered via a face or nasal mask, via nasopharyngeal tube with a water column (such as nasal bubble CPAP), or with a dedicated driver. The benefit of CPAP is that it delivers measurable positive airway pressure that is relatively easily controlled. While clinical experience suggests CPAP delivered via a nasal/facial mask is often poorly tolerated by infants and children, there are no studies to date which have examined this behavioural response in a critical care environment. However, compliance with CPAP in these populations indicates that their behavioural responses are likely to be similar to those observed in children with obstructive sleep apnoea.

Recently, a relatively new means of delivering non-invasive respiratory support has emerged, that of high flow nasal cannula (HFNC) or heated humidified high flow nasal cannula (HHHFNC) oxygen therapy. These terms are often used interchangeably within the literature, for the purpose of this thesis the acronym HFNC will be used. This new therapy allows the delivery of high inspired gas flows (with or without blended oxygen) that can be heated and humidified.
HFNC therapy is postulated to deliver a degree of CPAP, albeit uncontrolled and unpredictable, and may therefore help reverse some of the atelectasis that eventuates from respiratory illness.\textsuperscript{12-14} This has been the focus of many studies in neonatal and adult populations. However it is important to note that there is no universally agreed rate of flow for high flow in different patient age ranges. Factors which determine the rate of flow may be context dependent and this is somewhat determined by the devices used. Furthermore the majority of the studies have examined HFNC delivered in intensive care settings. While HFNC therapy is commonly used within the intensive care setting, the potential exists for its application in wards and emergency departments.

As a clinician, I have worked for the past 20 years in critical care environments, with the last 14 focused in paediatrics. I have had the opportunity to work in many different ICUs both nationally and internationally. In 2000, at the first paediatric ICU I worked in, most infants with bronchiolitis were intubated and mechanically ventilated. This changed dramatically with the introduction of HFNC therapy. In my current PICU, intubation and mechanical ventilation of infants with bronchiolitis decreased from 36% to 7% over a 5 year period.\textsuperscript{15} This potential to improve the clinical outcomes for infants, as a specific paediatric population, and to reduce the need for invasive ventilation has fascinated me, and lead me to question whether such a simple, and seemingly effective, paediatric intensive care therapy could also be safely used outside the high technology environment. The opportunity to explore the practical application of HFNC outside of the ICU and to acquire research skills concurrently was one I wholeheartedly embraced.

This research ultimately aimed to acquire, examine and disseminate knowledge that will assist the clinicians using HFNC therapy in managing infants with respiratory distress. The thesis that follows is the culmination of this research aim.

1.1 Overview of thesis

This thesis is presented in nine chapters. Figure 1 provides a schematic representation of the thesis, minus Chapter 9: references.

Chapter 2 provides an overview of bronchiolitis, its natural history, health service responses, and current and emergent treatment options.

Chapter 3 relates the proposed mechanism of action of HFNC and describes its use in the neonatal, adult and paediatric settings. It contains the case series publication.
Chapter 4 sets out a Cochrane review, with related publication incorporated.

Chapter 5 details the pilot study methodology.

Chapter 6 details the results of the pilot study with the related publication included.

Chapter 7 explores the implications of the findings of the systematic review, case series and pilot study as well as exploring the limitations of the thesis.

Chapter 8 details the conclusions of the thesis and provides recommendations for further research.

Chapter 9 is the list of references used throughout the thesis.

Figure 1.1 – Schematic representation of components and publications of the thesis
Chapter 2: Bronchiolitis

2.1 Introduction

The previous chapter introduced the components and reason behind embarking on this thesis. This chapter provides an overview of bronchiolitis, its natural history, health service responses, and current and emergent treatment options.

Bronchiolitis is the most common disease affecting infants less than two years of age, and is the leading cause of hospitalisation during the first year of life. It is characterised by a prodrome of symptoms, such as fever, cough, expiratory wheeze and rhinitis. The underlying pathophysiology is an acute inflammation of the terminal bronchioles and alveolar inflammation, typically viral in nature. While most infants experience a self-limiting illness and can be managed in the community, approximately 1–3% will require hospitalisation.

The treatment for bronchiolitis revolves around supportive care to maintain oxygenation, nutrition and fluid management. A wide variety of practices are employed among clinicians worldwide, using differing treatment options depending on the severity of the presenting illness. However, no one therapy has been proven to reduce the length of hospital stay or change the course of the disease process.

2.2 Natural history of bronchiolitis

The diagnosis of bronchiolitis is a clinical one. Infants will typically present with a history of coryzal symptoms; fever; wheezy cough; mild, moderate or severe respiratory distress; and on examination, have inspiratory crackles and/or expiratory wheeze. The duration of symptoms varies. Severity often increases in the first 72 hours with a return to baseline in around 2 weeks. Yet wheezing can continue for up to a month in some patients, and reactive airway disease can be seen into early adolescence. In addition, other conditions may present as bronchiolitis and differential diagnoses include: asthma, pneumonia or pneumonitis, congenital lung disease, cystic fibrosis, airway lesions, congenital heart disease and sepsis.

The most common virus associated with bronchiolitis is the respiratory syncytial virus (RSV). In the United States of America (US), RSV accounts more than 80% of all bronchiolitis cases. However other viruses such as influenza, parainfluenza and adenovirus may also have a causative role. Epidemics are usually seasonal in nature,
typically occurring in the winter months. In the southern hemisphere, incident peaks are observed in July\textsuperscript{29} and in the northern hemisphere incident peaks are observed in January and February.\textsuperscript{30} While the global burden of RSV disease is unknown, recent data suggest that it is not only the leading cause of acute lower respiratory infection (ALRI) for children less than 5 years of age, but also the main reason these children are hospitalised.\textsuperscript{31}

Exposure to RSV does not grant immunity, and reinfections are common throughout life.\textsuperscript{1} Prevalence studies from Europe suggest that 50\% of infants are infected with RSV before their first birthday, with 100\% infected by 2 years of age.\textsuperscript{32} In Australia, RSV is not a notifiable disease and therefore reliable data on the disease prevalence does not exist. However, it is reasonable to expect that prevalence would mirror the US and European evidence.

The determinants of hospitalisation vary from clinician to clinician and country to country, yet revolve around need for oxygen therapy and hydration.\textsuperscript{20,33} In one US study, the mean length of hospitalisation for uncomplicated bronchiolitis was 3.6 days, with a range of 1–17 days.\textsuperscript{33}

Infants with bronchiolitis can progress to develop symptoms of respiratory failure. It is estimated that 10–15\% of infants admitted to hospital with bronchiolitis go on to require intensive care for worsening respiratory distress.\textsuperscript{5,34} The underlying pathology includes an increase in mucus production and sloughing of necrotised epithelial cells, leading to decreased airway clearance. Along with mucosal oedema and inflammation of the small airways, this can lead to hypoxemia and hypercapnea. Symptoms of respiratory distress include an increased respiratory rate; substernal, subcostal, intercostal recession; head bobbing; grunting; air trapping; nasal flaring; apnoea; and thoracic-abdominal asynchrony.\textsuperscript{18,35}

Those infants and children who are immunocompromised, have chronic lung or congenital heart disease, or are premature, are at an even greater risk, not only of developing severe bronchiolitis, but requiring admission to intensive care, at rates as high as 36\%.\textsuperscript{5} Ethnic background also has an association between not only bronchiolitis but severity of disease, with increased hospital admission rates for infants from indigenous Australian, Maori and First Nation backgrounds.\textsuperscript{36–38} Within Australia and New Zealand, the mean length of stay in ICUs for infants with bronchiolitis is 3.37 days.\textsuperscript{39}
2.3 Health service response

In the US, bronchiolitis admissions are estimated to cost more than US$500 million annually,\textsuperscript{40} and when diagnoses of pneumonia are included, the cost almost doubles. The rates of hospitalisation for bronchiolitis have increased over time, doubling in the US from 1988 to 1996, with no change in mortality rates.\textsuperscript{41} Multiple factors may have influenced the increased rate of hospitalisation, including, greater detection of hypoxia via pulse oximetry\textsuperscript{33} lowered cut-off points for hypoxia and the administering of oxygen, increased survival of premature infants, prevalence of infants with chronic disease, and increased day-care attendance by children at younger ages.\textsuperscript{17,20,26,34}

In Australia, bronchiolitis results in approximately 16,000 admissions to hospital a year.\textsuperscript{42} It is also the most common reason for non-elective admission to Australian Paediatric Intensive Care Units (PICUs) and general ICUs, with over 850 admissions annually.\textsuperscript{39} Although it may be assumed that this places a substantial burden on our health care services, this claim is difficult to support – to date no estimate of quantified cost to the Australian health care system is available. While costs could be extrapolated from the US study, this would be misleading as health care systems significantly differ.

A recent report by The Australian Lung Foundation (2007)\textsuperscript{43} has, however, identified that respiratory infectious disease amongst all ages in Australia does place a significant burden on our health system, and is a major health priority. The report extrapolated costs based on US admission rates in 1991, and with these rates converted to the Australian environment, the cost would be A$20 million.\textsuperscript{43} Yet epidemiological studies on RSV and bronchiolitis remain limited in Australia.\textsuperscript{44} This would be a worthwhile area of investigation, along with the fiscal implications to the Australian health care system for both these conditions.

2.4 Sequelae

Encompassing bronchiolitis and pneumonia, ARLI are the leading worldwide cause of mortality and morbidity in young children (aged less than 5 years), with an incidence rate of 17\%.\textsuperscript{45} While hospitalised infants have a mortality of <1\%, it may be as high as 3.5\% in high-risk patients (those with chronic lung or heart disease, and prematurity).\textsuperscript{5} Within the UK, 2.9 deaths per 100,000 population are estimated per year in infants (less than 12 months) with a respiratory cause and RSV infection.\textsuperscript{46} In the US, mortality is estimated at 5.3 per 100,000 population.\textsuperscript{47} The Australian Bureau of Statistics (2002) reports postnatal mortality for 28 days to 1 year of age at 1.7 per 1,000 live births.\textsuperscript{48} Diseases of
the respiratory system account for 6.5% (of these total deaths) however neither bronchiolitis nor RSV is distinguished in these statistics, making it difficult to compare to other countries.

Post-discharge readmission is another objective sequelae. In a study by Norwood et al, the predictors of a possible readmission after first presentation to the emergency department were: age less than two months, prematurity of less than 35 weeks gestation, and a history of hospitalisation. Finally, a small number of infants are at risk of recurrent wheezing illnesses throughout their childhood due to early RSV infection.

2.5 Current treatment options

First-line treatment of bronchiolitis can be broadly classified into two distinct groups: pharmacologic and non-invasive respiratory support.

2.5.1 Pharmacological treatment options

Several pharmacological therapeutic options are used in the treatment of bronchiolitis. While they may offer short term relief of the symptoms, none have shown a clear benefit in altering the course of the disease, or modifying length of hospital stay. Most pharmacologic respiratory support aims to reduce either the inflammatory response, or to promote smooth muscle relaxation of the small airways. The eight major pharmacological treatment options are detailed in the following sections.

2.5.1.1 Bronchodilators

Bronchodilators administered as aerosols are used to relax the bronchial smooth muscle, reducing bronchospasm and bronchial hyper-reactivity, subsequently increasing the diameter of the airways. This modality is effective in children and adults with asthma. However, bronchiolitis is different as the airways are typically obstructed and oedematous, rather than constricted. Therefore infants and children with bronchiolitis are unlikely to respond to bronchodilators.

A Cochrane Collaboration systematic review of the use of bronchodilators (specifically albuterol, ipratropium bromide and adrenergic agents) found that while use in managing bronchiolitis was common, and short term improvements in clinical scores may occur, "bronchodilators cannot be recommended for routine management of first time wheezers who present with the clinical findings of bronchiolitis, either in the inpatient or outpatient settings". Part of this is due to increasing reports of adverse effects, such as tachycardia.
and tremors, reported in children and infants treated with bronchodilators. Uncertainty of their effectiveness also exists, especially with those presenting with a clinical picture of bronchiolitis and first-time wheezing. This is in addition to the high cost involved in using bronchodilators. To conclusively determine the efficacy of bronchodilators in the treatment of bronchiolitic infants, large multicentre controlled trials would be needed, in which infants and children with recurrent wheezing which may indicate asthma (and have a positive effect from bronchodilators) and infants with bronchopulmonary dysplasia would be excluded.

2.5.1.2 Adrenaline (epinephrine)

Adrenaline is a drug with both alpha and beta adrenergic properties. The rationale for using adrenaline to treat bronchiolitis is that the alpha adrenergic effects cause vasoconstriction, thereby reducing the oedema of the small airways. This mechanism could help reduce the symptoms of bronchiolitis.

A recent review assessed the evidence supporting the use of adrenaline and other bronchodilators (salbutamol), compared with a placebo, for treating infants less than 2 years of age with bronchiolitis. Bronchodilators have been proven to benefit children with asthma, and as both conditions produce symptoms of wheezing, it could be thought that these same drugs would work in a similar way in both conditions. However bronchiolitis and asthma are distinctly different and the effects of adrenaline on infants with bronchiolitis is less dramatic.

2.5.1.3 Glucocorticoids

Glucocorticoids are a class of steroid hormone. As bronchiolitis is associated with first-time wheezing, similar to asthma, the use of steroids was thought to potentially have similar benefits to those with acute asthma. However, it is now understood that bronchiolitis is a heterogeneous disease and distinctly different to asthma.

In a Cochrane Collaboration systematic review of children with bronchiolitis administered systemic or inhaled corticosteroids, no difference was found in hospitalisation rates, length of stay, readmission rates and clinical scores when compared with a placebo. However, a study where dexamethasone-epinephrine were administered in combination resulted in a reduction in hospitalisation within the 7 days following treatment. While a synergistic effect is postulated, subgroup analysis was inconclusive. Further research needs to be
carried out to clarify the efficacy, potential harm and applicability of combining these two therapies.53

2.5.1.4 *Heliox*
In bronchiolitis, a critical narrowing of small airways results in turbulent flow, increased airway resistance, and ventilation/perfusion mismatch.55 Helium has a lower density compared to air and may improve gas flow through high resistance airways by making the flow more laminar.56 While it has no anti-inflammatory or bronchodilatory properties, helium can aid in increasing oxygen flow to the alveoli, and decrease the work of breathing.57 Also, carbon dioxide (CO₂) diffuses through helium four times faster than air, aiding in CO₂ removal and consequently ventilation.55 However, a review of the current literature reveals that when heliox (helium-oxygen mixture) is administered, there is no reduction in the need of mechanical ventilation, intubation or PICU length of stay.55

2.5.1.5 *Antibiotics*
Antibiotics are not recommended for treating bronchiolitis unless an indication of secondary bacterial infection is present.22 Therefore, antibiotics being prescribed in 34–99% of uncomplicated bronchiolitis cases is surprising.58 A systematic review by Spurling et al58 concludes that antibiotics may be justified in children with bronchiolitis who worsen and develop respiratory failure, however further research is warranted to determine the subgroup of patients who may benefit.

2.5.1.6 *Nebulised 3% saline (hypertonic saline)*
Hypertonic saline works by decreasing the viscosity of the mucous in the airways. It has been shown to be effective in patients with cystic fibrosis, asthma, bronchiectasis and sino-nasal disease.59 Benefits seen in these patients may also be expected in infants with bronchiolitis – hypertonic saline may help reverse some of the pathophysiological abnormalities by rehydrating the airway surface thereby improving mucous clearance; lowering the viscosity and elasticity of the mucous; reducing airway oedema; and inducing coughing to help clear secretions and relieve obstruction of the upper airways.60

A meta-analysis showed a significantly shorter length of hospital stay and lower clinical severity scores in those infants already hospitalised with non-severe acute bronchiolitis, and treated with hypertonic saline.59 Treatment regimes in terms of optimal delivery times, duration of treatment, and saline concentration remain to be evaluated. Large multicentre trials are required to further evaluate the effectiveness of this therapy.59
2.5.1.7 Ribavirin

Ribavirin is an antiviral agent that can be administered by aerosol. In in vitro studies,\(^6^1\) it seems to produce good activity against the viruses causing bronchiolitis, however more recent studies have shown no clear benefit,\(^6^2\) and the American Academy of Pediatrics (2006)\(^1\) has recently recommended against its routine use. As an aerosol, Ribavirin can be cumbersome to use, is high in cost, may have teratogenic effects for caregivers, and haemolytic side effects for patients.\(^2^1\) However, it may be considered for high-risk patients (immunocompromised, and those with significant cardiopulmonary disease).\(^1\)

2.5.1.8 Surfactant

The use of surfactant in pre-term infants with primary surfactant deficiency is known to reduce mortality and the incidence of air leak syndrome.\(^6^3\) Due to the pathophysiological changes in the airways of infants and children with severe bronchiolitis, and the changes that occur with mechanical ventilation, there is the possibility of secondary surfactant deficiency, which could prolong recovery time, and increase the length of stay in the ICU and within the hospital.\(^6^2\) Administering surfactant in pre-term infants has proven successful, and it is plausible that the same would be true in viral bronchiolitis. However, a Cochrane Collaboration systematic review found that while the administration of surfactant may be reasonably safe, the limited data and heterogeneity of the trials makes it difficult to draw strong conclusions, and further studies are required.\(^6^4\)

2.5.2 Summary of pharmacological treatment options

Pharmacological treatments for bronchiolitis employ agents that attempt to address either the issue of airway inflammation, or to relax the smooth muscles of the airways. Internationally there is variation in the use of the clinical markers (crackles, wheeze and age) to distinguish between bronchiolitis, early asthma and reactive airway disease presentations.\(^2^0\) This can explain some of the commonality in treatment modalities between the different diagnoses. While no one treatment is entirely effective in shortening the course of the disease or length of hospital admission, there may be potential benefits with the combination of dexamethasone and epinephrine. However, all studies and systematic reviews of studies acknowledge that further investigation into the use of these treatments is warranted to provide clinicians with more comprehensive evidence to support their practice.
2.5.3 Non-invasive respiratory support
Options to reduce work of breathing include non-invasive methods of respiratory support. Traditionally these range from steam inhalation, to CPAP administered with a facial/nasal mask interface, connected to a ventilator or to a specific driver. Evidence relating to five means of non-invasive respiratory support is detailed in the following sections.

2.5.3.1 Steam inhalation
The rationale for using steam inhalation (or cool mist therapy) is that steam acts as a secretolytic agent, making secretions easier to expel from the respiratory tract and relieving respiratory distress. While this sounds plausible, a Cochrane Collaboration systematic review found only one study for inclusion, although they noted a number of methodological weaknesses. The included study found no difference in respiratory distress symptoms in those patients treated in a mist tent compared with a placebo (nebulised saline). The review concluded there was insufficient evidence to inform practice and further trials should be considered.

2.5.3.2 Chest physiotherapy
The aim of chest physiotherapy in bronchiolitis is to clear the airways of obstruction, and by doing so enhance gas exchange and reduce the work of breathing. Techniques used in paediatric patients include chest percussion, vibration, postural drainage, directed coughing, and passive forced expiration. The techniques and use of this therapy vary between countries and regions, so there is no standard use in bronchiolitis. A Cochrane Collaboration systematic review of chest physiotherapy in bronchiolitis draws the conclusion that the evidence is weak both for and against its use. The specific techniques of vibration and percussion were not shown to decrease length of hospital stay or improve the clinical severity score. However, in a subsequent study using a different physiotherapy method that included nebulised hypertonic saline, improvement was observed in the infants' clinical severity scores. The recommendation from this trial is for further multicentre studies to confirm the preliminary results.

2.5.3.3 Continuous positive airway pressure (CPAP)
Infants with severe bronchiolitis have the potential to develop severe respiratory distress, apnoea and hypoxia, and regional atelectasis of the lung is a common feature in infants breathing near their closing volume. CPAP can reduce the work of breathing and
improve functional residual capacity, potentially avoiding intubation. This level of respiratory support is usually administered in a dedicated ICU setting.

A retrospective study reported the use of non-invasive ventilation for treating severe bronchiolitis over two winter seasons. In the second season where non-invasive ventilation was primarily used, there was a shorter duration of oxygen therapy required and fewer cases of ventilator associated pneumonia. However, the retrospective design and small sample size (winter 1, n= 53 and winter 2, n=27) necessitates cautious consideration of the findings.

The underpowering of studies was highlighted in a recent systematic review evaluating CPAP. Five studies were included for assessing CPAP, with only one being a randomised controlled trial. While individual studies reported potential benefits of CPAP in preventing endotracheal intubation for severe bronchiolitis, this outcome could not be substantiated in the review. Therefore, the role of this supportive therapy is still undetermined. This result is further supported by similar conclusions in a Cochrane Collaboration systematic review into CPAP for acute hypoxemic respiratory failure in children. Overall, there remains a lack of large, well designed, controlled trials to evaluate the role, risks and benefits of non-invasive modes of respiratory support.

2.5.3.4 CPAP and heliox
The use of heliox in combination with CPAP may decrease the work of breathing. Heliox can overcome airway resistance, a feature of bronchiolitis, due to the increased laminar flow of gas. This treatment may improve oxygenation and the removal of carbon dioxide, with CPAP helping to keep these airways open. Again, from a systematic review of the literature, the benefits of heliox and CPAP cannot be evaluated due to underpowered studies.

2.5.4 Summary of non-invasive respiratory support
Non-invasive forms of respiratory support for bronchiolitis employ techniques, including CPAP, to overcome airway resistance and support the work of breathing. However no one study can draw definitive conclusions about the benefits and risks of each therapy described. All therapies need further study to provide the power necessary to inform clinical practice.
2.5.5 Emergent treatment – high flow nasal cannula

One of the drawbacks with CPAP delivered via a nasal/facial mask is that it is often poorly tolerated by infants and children.\textsuperscript{80} A relatively new system in delivering non-invasive respiratory support has emerged, that of high flow nasal cannula (HFNC) therapy. This treatment option is the focus of this thesis and is considered in more depth in the next chapter.

2.6 Conclusion

This chapter has summarised bronchiolitis and identified it as the most common ALRI in infants aged less than two years. Admission rates to hospitals in high income countries are increasing, which places a substantial burden on any health care budget. Management approaches, which vary throughout the world, with no clear evidence for any single treatment approach, have been described.\textsuperscript{34} While systematic reviews have assessed a wide variety of therapies – and found potential benefit with nebulised hypertonic saline, surfactant, and epinephrine/dexamethasone combinations – there remains no one standout treatment for infants with bronchiolitis. Further investigation with larger, well-conducted, multicentre controlled trials is still required to evaluate many of these therapies. The mainstay of treatment remains supportive care in the form of supplemental oxygen and hydration, with no singular routine treatment recommended.\textsuperscript{1}

HFNC oxygen delivery may offer an alternative mode of treatment for bronchiolitis. This is an area that deserves further investigation to provide good quality evidence to further inform clinician practice and treatment options for this disease. The next chapter will present what is currently known about HFNC therapy across the age spectrum.
Chapter 3: High flow nasal cannula therapy

3.1 Introduction

The preceding chapter detailed the cohort of paediatric patients most likely to require an admission to hospital, those with bronchiolitis, and examined the available treatment options. This chapter details the mechanism of action for HFNC therapy, and the studies that have been undertaken across patient age groups, from pre-term neonates to adults.

Simple nasal cannula is one of the most frequently used methods to deliver supplemental oxygen to patients with hypoxemia. This common interface has been in use since the 1940s, however, lack of humidification restricts the flow rates that can be delivered.\textsuperscript{12,81} This can result in an inability to match a patient's spontaneous inspiratory flow rate, leading to worsening respiratory distress. In contrast, some systems – termed HFNC – can deliver higher flows of heated and humidified oxygen-gas mixtures. These have the potential to meet or exceed a patient's spontaneous inspiratory flow, thereby reducing their respiratory distress.\textsuperscript{82}

While ‘high flow’ rates have been studied as far back as 1994,\textsuperscript{83} neonatal ICUs have advanced clinical usage over the past 10 years as an alternative respiratory support mode to nasal CPAP.\textsuperscript{84} Therefore, high flow delivery systems have been increasingly used across a wide range of age groups of patients with respiratory distress.

3.2 Mechanism of action

While the clinical use of HFNC therapy is rapidly growing, the exact mechanism through which it works remains unclear. There is increasing physiological evidence that supports the postulation by Dysart et al\textsuperscript{12} that there are a number of factors that influence the mechanism of action of HFNC therapy.

3.2.1 Washout of nasopharyngeal dead space

The first postulated mechanism of action is that HFNC therapy washes out anatomical nasopharyngeal dead space. This would reduce dead space overall and provide a physiological explanation for improved alveolar ventilation and respiratory effort.\textsuperscript{12,85} Tracheal gas insufflation (TGI) has been used as a comparison for this mechanism of dead space washout. TGI uses a catheter inserted into an artificial airway or specially designed endotracheal tube to use fresh gas to flush the mechanical dead space.\textsuperscript{86} The
additional flow during mechanical ventilation reduces volume and pressure requirements and facilitates pulmonary gas exchange, namely CO₂ elimination.\textsuperscript{87–90}

HFNC therapy is purported to have an effect on dead space due to improved ventilation rates. The study by Dewan and Bell\textsuperscript{83} compared high and low flows through regular nasal cannula and transtracheal catheters (TTC) in patients with chronic obstructive airways disease (COPD). The use of high flows (3-8 L/min) provided greater exercise tolerance, but of interest is that delivery via nasal cannula (at higher flows) was just as effective for dead space washout as via TTC.\textsuperscript{83}

A recent neonatal animal study supports this view. After inducing a lung injury on piglets, they were supported on HFNC therapy with increasing flows from 2 L/min up to 8 L/min. Results indicated that gas exchange was improved in a flow dependent manner. Increased carbon dioxide clearance and improved oxygenation enhanced overall ventilation. It was also noted that at 8 L/min, tracheal pressures did not exceed 6±1 cm H₂O, making it comparable to conventional CPAP.\textsuperscript{85}

### 3.2.2 Reduction in work of breathing

A second postulated mechanism is that HFNC therapy reduces the overall work of breathing (WOB). This may be through either stenting of the airways or through higher flow rates that either match, or exceed, a patient's peak inspiratory flow, and hence minimise the inspiratory resistance associated with the nasopharynx.\textsuperscript{12,86}

In a study by Miller et al\textsuperscript{91} it was demonstrated that CPAP reduced supraglottic resistance in the premature infant by 29 cmH₂O/L. The reduction in resistance was postulated as being due to positive pressure effectively stenting the airways open.

Saslow et al\textsuperscript{65} demonstrated that premature neonates supported with flow rates of 3-5 L/min had similar WOB compared to nasal CPAP at 6cmH₂O. More recent clinical studies of neonates and children, using objective measuring techniques such as oesophageal or nasopharyngeal pressures, have demonstrated that increasing flow rates (1–8 L/min flow range) are associated with improved breathing patterns in these patients.\textsuperscript{92–94}

### 3.2.3 Delivery of warmed and humidified gas

Another important mechanism is HFNC’s effect on respiratory mechanics from the delivery of warmed and humidified gas. A study focusing on epithelial cells demonstrated that low
humidity or dry gas was detrimental to cells, resulting in increased inflammation and reduced cell function. In addition, dry, cold gas has been shown to elicit a bronchoconstrictive response in asthmatics and normal subjects. Humidification from HFNC therapy ameliorates this effect, demonstrating that adequate conditioning (warming and humidifying) of the airways does have a beneficial physiological effect.

3.2.4 Positive distending pressure

Finally, HFNC therapy is postulated to provide positive airway pressure (PAP). The benefit of PAP is that it can help recruit alveoli and maintain alveolar patency, subsequently reducing ventilation-perfusion mismatch. PAP has been inferred in these studies by using objective measures taken from a variety of sites including the oral cavity, nasopharyngeal, tracheal and oesophageal areas. As a partial consequence, the generated pressure reported varies, ranging from 2–8 cmH₂O.

The amount and effect of any positive pressure generated with HFNC can be influenced by a variety of factors. Kubicka et al demonstrated in infants (weight 835-3735gm) that pressure was only generated with a closed mouth. It was also determined that there was a linear relationship between the pressures generated, flow and weight of the infant. Urbano et al showed similar findings in a paediatric airway model. A linear relationship was shown in the pressure measured in the pharynx and airway with increasing flow rates (5-20 L/min with maximal pressure 4cmH₂O) with the mouth closed. This was lost with an open mouth, regardless of the flow rate. In a study on infants with bronchiolitis, Arora et al also showed that there were significant differences in nasopharyngeal pressures generated between open and closed mouth states, yet they determined that a linear relationship was only apparent between flow and pressure generated, not weight of the infant.

The linear relationship between flow rate and pressure generated has been demonstrated in adult studies. Groves and Tobin measured flow rates (up to 60 L/min) on health adult volunteers. With increasing flow rates, increased pressure was generated, but the pressure generated was higher in a closed mouth state. The study by Parke et al showed similar findings, with pressure increasing with increasing flow, and greater pressure generated with the mouth closed. A physical (test lung model) study by Hasan and Habib further showed that pressure delivered is also affected by the nares-prong interface. Moderate leak around the nares resulted in lower upper airway pressures.
While many studies have demonstrated that HFNC therapy delivers positive pressure, it is unlikely to be above 8cmH2O\(^1\) and is compromised with the mouth being open and leakage around the nares.

### 3.2.5 Summary of mechanism of action

There continues to be a lack of universal agreement on the exact mechanism of action of HFNC therapy. It has an ability to match inspiratory demands; wash out nasopharyngeal dead space; and generate, albeit unpredictably and uncontrollably, positive airway pressure (in the absence of leak around nares and mouth). Yet its use in clinical settings is increasing possibly due to its ease of use and application, patient tolerance and the perceived theoretical clinical benefits.

### 3.3 HFNC therapy in pre-term to term neonates

Several systematic reviews have assessed the evidence for using HFNC therapy as respiratory support in pre-term infants.\(^86,106–108\) Here, however, a dilemma arises in assessing the studies due to the heterogeneity in study design, participants, intervention, comparators, and primary and secondary outcome measures. While HFNC therapy has predominantly been compared to nasal CPAP in pre-term infants,\(^109\) other studies compared HFNC therapy to low flow nasal oxygen therapy,\(^110,111\) or another form of HFNC therapy.\(^112\) In those trials comparing HFNC therapy to nasal CPAP, the clinical context for its use varies: as an alternative to CPAP post-extubation,\(^106\) as support for respiratory distress instead of CPAP,\(^113\) and in weaning off CPAP.\(^114\) Yet, some studies only report the physiological effects of HFNC\(^13,82,99\) and fail to include important clinical measures such as the need for intubation/re-intubation. Designs ranged from randomised controlled trials (RCTs),\(^106,110,112–114\) to observational\(^13,82,84,99,101,115\) and retrospective\(^116,117\) studies (Table 3.1). Of the 16 studies the high flow interventions varied considerably, with flow rates ranging from 0.5 L/min to a maximum of 8 L/min

The Cochrane Review by Wilkinson et al\(^107\), defined 'high flow' as rates >1 L/min, and identified four small RCTs that compared HFNC with other modes of respiratory support. Due to the heterogeneity of outcome measures and interventions, a meta-analysis was inappropriate. The overall conclusion was that there was insufficient evidence to determine the safety and efficacy of HFNC therapy compared to other forms of respiratory support for premature infants.
A subsequent systematic review in 2012, which included study designs beyond RCTs, found 19 studies to assess, of which 16 were clinical. While it found that distending pressures generated by HFNC therapy increased with increasing flow rates, there was still a lack of clarity in determining the safety and efficacy of this treatment option for premature infants.

Another review in 2013, assessing HFNC studies from neonates to adults, appraised eight neonate-specific studies. In respect to the neonatal studies reviewed, the authors determined that there was no definitive data supporting the use of HFNC therapy over CPAP in neonatal respiratory distress.

Despite all these reviews demonstrating an increasing use of HFNC therapy in nurseries globally, there remains inadequate evidence to fully endorse the safety or efficacy of this treatment. Large RCTs are needed, with consistency in design, methods, interventions, outcomes measured, and the type of HFNC device used. While earlier studies may have used unheated HFNC, more recent studies demonstrate that heated and humidified HFNC systems are the norm, and as such should be considered in any future study design.

### 3.4 HFNC therapy in adults

While the first published study on HFNC therapy was described in an adult population in 1994, a paucity of clinical studies have been undertaken since. Three systematic reviews have assessed the available evidence, showing that to date, there are only two RCTs, six retrospective/prospective observational studies, three case studies, and two physiological studies on healthy adult volunteers (Table 3.2). Of note is that while neonatal studies used NCPAP as the comparative therapy for HFNC, adult studies used low flow nasal cannula or face mask oxygen therapy. Of the 16 studies the high flow interventions varied considerably, with flow rates ranging from 15 L/min to 60 L/min. The common findings amongst the adult studies are that HFNC therapy may optimise oxygenation for patients with moderate hypoxaemic respiratory failure, HFNC is comfortable, and the need for escalation to other forms of support can be detected within 60–90 minutes of application.

Again, however, limited evidence exists to support the claim that ventilation is improved, and further research is required to both evaluate HFNC therapy effectiveness in the adult population, and provide evidence-based guidance for clinical application.
<table>
<thead>
<tr>
<th>Author</th>
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<td>Locke&lt;sup&gt;118&lt;/sup&gt;</td>
<td>1993</td>
<td>Observational</td>
<td>n=13 neonates, mean GA 30 weeks, mean BW 1377g</td>
<td>Unheated non-humidified HFNC at flow rates 0.5–2 L/min. Two prongs at 0.2 cm &amp; 0.3 cm</td>
<td>Oesophageal pressure monitored. No pressure generated at any flow with small prongs. Larger ones delivered increasing pressure with increasing flow.</td>
<td>Mean pressure of 9.8 cmH₂O at 2 L/min.</td>
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<td>Sreenan&lt;sup&gt;84&lt;/sup&gt;</td>
<td>2001</td>
<td>Observational</td>
<td>n=40 neonates, mean PCA 30.3 weeks, mean weight 1260 g</td>
<td>Unheated, humidified HFNC vs NCPAP. Flow rates 1–2.5 L/min</td>
<td>Oesophageal pressure monitored. No difference in frequency or duration of apnoeas.</td>
<td>Formula to predict flow required for pressure of 6 cmH₂O = 0.92 + (0.68 x infant weight).</td>
</tr>
<tr>
<td>Campbell&lt;sup&gt;113&lt;/sup&gt;</td>
<td>2006</td>
<td>Prospective RCT</td>
<td>n=40 neonates, mean GA 27 weeks, ≤1250 g, previously intubated</td>
<td>Unheated, humidified HFNC (1.4–1.7 L/min) vs NCPAP (5–6 cmH₂O)</td>
<td>Significantly higher rate of re-intubation with HFNC vs NCPAP within 7 days. HFNC group had higher rate of apnoeas and bradycardias, and increased oxygen use.</td>
<td>No difference in trauma to nares.</td>
</tr>
<tr>
<td>Woodhead&lt;sup&gt;112&lt;/sup&gt;</td>
<td>2006</td>
<td>Prospective randomised crossover trial</td>
<td>n=30 neonates, mean GA 32 weeks, previously intubated</td>
<td>24 hours of HHHFNC or unheated non-humidified HFNC (standard). Mean flow 3.1 L/min</td>
<td>Higher re-intubation rate in standard HFNC. No difference in RR at 24 hours. Lower incidence of nasal trauma and respiratory effort in HHHFNC.</td>
<td>Comparator not relevant now as HFNC systems are heated and humidified.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Notes</td>
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<tr>
<td>Saslow 82</td>
<td>2006</td>
<td>Observational, crossover study</td>
<td>n=18 neonates, GA 28 weeks, &lt;2 kg with mild RDS</td>
<td>HHHFNC (3–5 L/min) vs NCPAP (6 cmH₂O)</td>
<td>No difference in work of breathing and RR at any flow rate; pressure did not vary until 5 L/min.</td>
<td>Physiologic study, no clinical outcomes measured.</td>
</tr>
<tr>
<td>Shoemaker 117</td>
<td>2007</td>
<td>Retrospective, descriptive</td>
<td>n=101 neonates, mean GA 28.1 weeks (era 1), GA 27.6 weeks (era 2)</td>
<td>HHHFNC (n=65) vs NCPAP (n=36), Flow rate 5.2–8 L/min</td>
<td>Lower re-intubation rates and days ventilated in HHHFNC group. HHHFNC well tolerated.</td>
<td>No difference in adverse outcomes following introduction of HHHFNC.</td>
</tr>
<tr>
<td>Spence 99</td>
<td>2007</td>
<td>Observational</td>
<td>n=14 (6 studied on both HFNC &amp; CPAP, 2 studied on CPAP only, 6 studied on HFNC only) neonates, median GA 30 weeks, median weight 1589 g</td>
<td>HFNC 1–5 L/min (n=12) vs NCPAP 2–6 cmH₂O (n=8)</td>
<td>Intrapharyngeal pressures measured. HHHFNC pressure increased with increasing flow.</td>
<td>No comparison between pressures generated on HFNC and NCPAP.</td>
</tr>
<tr>
<td>Holleman-Duray 116</td>
<td>2007</td>
<td>Retrospective</td>
<td>n=114 neonates, mean GA 27 weeks, mean weight 1000 g, with RDS and extubated</td>
<td>HHHFNC 4–6 L/min (n=65) vs NCPAP (n=49)</td>
<td>No major differences in outcomes or oxygen use. Infants extubated to HHHFNC spent less days on ventilator and had lower ventilator rate.</td>
<td>Early extubation protocol in place during HHHFNC period.</td>
</tr>
<tr>
<td>Jasin 139</td>
<td>2008</td>
<td>Case study</td>
<td>n=1 neonate, GA 26 weeks, BW 901 g</td>
<td>Extubated to 4 L/min HHHFNC at 20 days, weaned to 2 L/min HHHFNC at 36 days.</td>
<td>Scalp emphysema, pneumo-orbitis and pneumocephalus noted and HHHFNC ceased on day 36 of life.</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Mode</td>
<td>Pressure Monitor</td>
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</table>
| Wilkinson¹¹⁵      | 2008 | Observational| 18 neonates, median PCA 33.6, median weight 1619 g | HHHFNC 2–8 L/min | Pharyngeal pressure monitored. Pressure increased with increased flow; inverse relationship between weight and pressure; mouth position irrelevant. Formula to predict pressure made: \( P(\text{cmH}_2\text{O}) = 2.6 + (0.8 \times \text{flow rate}) - (1.4 \times \text{infant weight}) \).
| Kubicka¹⁰¹       | 2008 | Observational| 27 neonates, PCA range 29.1–44.7 weeks, weights 835–3735 g | HHHFNC, Vapotherm (n=16) and F&P (n=11) | Oral pressure monitored. No pressure generated with mouth open; pressure increased with flow (infants <1500 g) with mouth closed.
| Lampland¹³       | 2009 | Observational| 15 neonates, mean GA 29.5 weeks, mean weight 1324 g | HHHFNC 1–6 L/min vs NCPAP 6 cmH₂O | Oesophageal pressure monitored. RR rate increased as flow rate decreased. Pressure increased with increasing flow. Other physiological parameters did not differ.
| Miller¹¹⁰        | 2010 | Prospective RCT | 40 neonates, mean GA 28 weeks, previously intubated | Vapotherm vs Fisher & Paykel HHHFNC. Flow rate 6 L/min | No statistical difference in rate of failure; Vapotherm group 9%, F&P group 18%, at 72 hours.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Type</th>
<th>Study Details</th>
<th>Results</th>
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</table>
| Abdel-Hardy\textsuperscript{114} | 2011 | Prospective RCT | n=60 neonates, mean GA 31 weeks, mean weight 1600 g
Weaning from NCPAP with/without weaning to HHHFNC. Flow rate 0.5–2 L/min | No difference in success of weaning from NCPAP. Sustained NCPAP had fewer days on supplemental O\textsubscript{2} and shorter duration of respiratory support. 63% of infants on HHHFNC did not require FiO\textsubscript{2} >0.21. |
| Manley\textsuperscript{140} | 2012 | RCT, multicentre, non-inferiority | n=303 neonates, mean GA 27 weeks, mean weight 1041 g
HFNC (5–6 L/min) vs NCPAP (7 cmH\textsubscript{2}O) after extubation | HFNC was non-inferior to NCPAP, with treatment failure occurring in 34.2% of HFNC group and 25.8% in NCPAP. 17.8% infants’ re-intubated in HFNC compared to 25.2% in NCPAP. Almost half the infants failing HFNC were successfully treated with NCPAP. Nasal trauma significantly reduced in HFNC group, no differences in adverse events or other complications between groups. |
| de Jongh\textsuperscript{94} | 2014 | Observational, crossover study | n=20 neonates, mean PCA 32 weeks, mean weight 1516 g
HHHFNC (3–5 L/min) and NCPAP (5–6 cmH\textsubscript{2}O) | RIP used to measure WOB. HHHFNC is comparable to NCPAP as a viable non-invasive mode of respiratory support. |

CPAP = continuous positive airway pressure; NCPAP = nasal CPAP; HFNC = high flow nasal cannula; HHHFNC = heated and humidified, high flow nasal cannula; GA = gestational age; PCA = post conceptual age; BW = birth weight; F&P = Fisher & Paykel Healthcare; RIP = respiratory inductive plethysmography; WOB = work of breathing; RDS = respiratory distress syndrome; RCT = randomised controlled trial
Table 3.2 – Adult studies with HFNC therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Participants (n=)</th>
<th>Comparator/Intervention</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dewan</td>
<td>1994</td>
<td>Prospective observational</td>
<td>n=10 patients with COPD, in clinic</td>
<td>High flow trans-tracheal oxygen (mean 5.1 L/min) vs low flow trans-tracheal oxygen (mean 1.05 L/min); and HFNC (mean 5.9 L/min) vs LFNC (mean 1.62 L/min)</td>
<td>Exercise distance with HFNC was 2.38 times greater than LFNC; no difference in dyspnoea scores with HFTTO and HFNC.</td>
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</tr>
<tr>
<td>Chatila</td>
<td>2004</td>
<td>Non-randomised crossover</td>
<td>n=10 stable COPD, in outpatient clinic</td>
<td>HFNC (Vapotherm) at 20 L/min vs low flow, non-humidified O₂ at 2.5–6 L/min</td>
<td>Significant improvement in PaO₂ and SpO₂ during exercise with HFNC. No significant improvement at rest with low flow.</td>
<td>Only half of patients were able to complete both exercise periods (12 minutes).</td>
</tr>
<tr>
<td>Groves</td>
<td>2007</td>
<td>Observational</td>
<td>n=10 healthy individuals</td>
<td>HFNC (F&amp;P) with flows 0–60 L/min</td>
<td>Pharyngeal pressure monitored. Significant positive pressure generated, linear relationship with flow, and dependent on mouth open/closed.</td>
<td></td>
</tr>
<tr>
<td>Calvano</td>
<td>2008</td>
<td>Case study</td>
<td>n=1 elderly dementia patient with severe hypoxaemia, in ICU</td>
<td>HFNC (Vapotherm)</td>
<td>HFNC improved gas exchange, dyspnoea and was well tolerated; marked improvement in quality of life.</td>
<td>Unable to tolerate face mask. Patient was for palliative care.</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Study Design</td>
<td>Patient Details</td>
<td>Intervention</td>
<td>Findings</td>
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<tr>
<td>Price142</td>
<td>2008</td>
<td>Prospective audit</td>
<td>n=72 patients, majority with hypoxaemic respiratory failure, in HDU</td>
<td>HFNC (Vapotherm)</td>
<td>No significant improvements in baseline PaO₂, arterial O₂ saturation or RR.</td>
<td></td>
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<tr>
<td>Roca132</td>
<td>2010</td>
<td>Prospective sequential intervention</td>
<td>n=20 patients with ARF in ICU</td>
<td>HFNC (30 L/min) vs face mask oxygen (15 L/min)</td>
<td>Less dyspnoea and mouth dryness, more comfortable on HFNC. Higher PaO₂ and lower RR on HFNC. Self-evaluation of patient comfort after 30 min of each therapy.</td>
<td></td>
</tr>
<tr>
<td>Tiruvoipati128</td>
<td>2010</td>
<td>Prospective randomised crossover</td>
<td>n=50 patients post-extubation in ICU</td>
<td>HFNC (F&amp;P) 30 L/min vs face mask 30 L/min</td>
<td>No significant difference in SpO₂, ABG and patient comfort. Tolerance significantly better with HFNC.</td>
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</tr>
<tr>
<td>Parke98</td>
<td>2011</td>
<td>Prospective RCT</td>
<td>n=60 patients with mild–moderate hypoxaemia in ICU</td>
<td>HFNC vs face mask</td>
<td>Fewer treatment failure and desaturations in HFNC group. Flows from face mask not reported.</td>
<td></td>
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<tr>
<td>Sztrymf130</td>
<td>2011</td>
<td>Prospective pilot study</td>
<td>n=38 patients with hypoxaemic respiratory failure non-responsive to NRB mask, in ICU</td>
<td>HFNC (mean 49 L/min)</td>
<td>Improved PaO₂ and PaO₂/FiO₂ at 1 and 24 hr, decreased RR, HR and WOB up to 48 hr with HFNC. 9 HFNC were intubated; did not decrease clinical signs at 1 hr. Well tolerated.</td>
<td></td>
</tr>
<tr>
<td>Corley134</td>
<td>2011</td>
<td>Observational</td>
<td>n=20 post-cardiac surgical patients with respiratory distress, in ICU</td>
<td>HFNC (35–50 L/min) vs nasal cannula/face mask (variable flow)</td>
<td>Oropharyngeal pressure and EELI measured. HFNC generated 3±1.2 cmH₂O. RR, dyspnoea score and PaO₂/FiO₂ ratio improved.</td>
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</tr>
<tr>
<td>Boyer135</td>
<td>2011</td>
<td>Case study</td>
<td>n=1 with pulmonary fibrosis and ARF, in ICU</td>
<td>HFNC at 40 L/min</td>
<td>Improved PaO₂, well tolerated. Was able to discharge home and palliated.</td>
<td></td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Patients</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Notes</td>
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<tr>
<td>Carratala</td>
<td>2011</td>
<td>Case study</td>
<td>n=5 elderly patients with acute heart failure and pulmonary oedema, in ICU</td>
<td>HFNC (F&amp;P) up to 60 L/min</td>
<td>Analysis at 24 hours post-HFNC. Significant reduction in RR and increase in PaO&lt;sub&gt;2&lt;/sub&gt; post-HFNC.</td>
<td>All treated in ED with non-invasive ventilation prior to HFNC. High degree of patient comfort.</td>
</tr>
<tr>
<td>Sztrymf</td>
<td>2012</td>
<td>Prospective observational</td>
<td>n=20, patients with ARF in ICU</td>
<td>HFNC (32–50 L/min) vs non re-breathing mask (9–15 L/min)</td>
<td>Improved RR, SpO&lt;sub&gt;2&lt;/sub&gt; and PaO&lt;sub&gt;2&lt;/sub&gt; immediately after HFNC, sustained up to 12 hours.</td>
<td>6 patients from HFNC intubated</td>
</tr>
<tr>
<td>Lenglet</td>
<td>2012</td>
<td>Prospective observational</td>
<td>n=17 patients with hypoxaemic respiratory failure non-responsive to NRB mask, in ED</td>
<td>HFNC (F&amp;P) used following failure of non-rebreather reservoir mask therapy</td>
<td>Decreased RR, improved dyspnoea score, and increased SpO&lt;sub&gt;2&lt;/sub&gt; with HFNC use.</td>
<td>Noise from HFNC similar to non-rebreather mask and ambient department.</td>
</tr>
<tr>
<td>Peters</td>
<td>2012</td>
<td>Retrospective</td>
<td>n=50 patients with do-not-resuscitate, in ICU</td>
<td>HFNC (F&amp;P) used for hypoxic respiratory distress</td>
<td>Improvement in SpO&lt;sub&gt;2&lt;/sub&gt; and RR, 18% escalated to NIV.</td>
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<tr>
<td>Mundel</td>
<td>2013</td>
<td>Randomised, controlled, crossover study</td>
<td>n=10 healthy individuals</td>
<td>HFNC (F&amp;P) at flows 15, 30 and 45 L/min</td>
<td>RIP measured. Increase in tidal volume and decreased RR during wakefulness. During sleep, 20% fall in minute ventilation (Vt decrease not RR).</td>
<td>4 x 60 minute visits, one week apart, during wakefulness and sleep. Nasal cavity model used to compare with CPAP during simulated breathing. Mechanism of action different between the two.</td>
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</tbody>
</table>

HFNC = high flow nasal cannula; LFNC = low flow nasal cannula; HFTTO = high flow trans-tracheal oxygen; EELI = end expiratory lung impedance; ARF = acute respiratory failure; F&P = Fisher and Paykel Health Care-Optiflow system; NRB = non-rebreather; ED = emergency department; ICU = intensive care unit; HDU = high dependency unit; RIP = respiratory inductive plethysmography; Vt = tidal volume
3.5 HFNC therapy in infants and children

Within the paediatric population (ages one month to 16 years), evidence from RCTs is even more limited than for adults and neonates, with only one published RCT. The remaining studies comprise retrospective cohort reviews, or prospective observational studies (Table 3.3). Of the 17 studies the high flow interventions varied considerably, with flow rates ranging from 1L/min to 8 L/min. However, one systematic review, limited to infants with bronchiolitis, identified six ongoing RCTs. In future these may add to the evidence base.

Importantly, four studies distinguish 'responders' to HFNC therapy from 'non-responders', suggesting that specific clinical indicators may be useful in predicting success of the therapy, and in a timely manner. Key clinical indicators identified are respiratory rate and heart rate, and those who 'respond' to HFNC therapy do so with a significant decrease (20%) from initial baseline in these parameters within 60–90 minutes of starting therapy. This may be clinically important in reducing the risk of delay in escalating respiratory support, and mitigating potential sequelae as a result of the delay.

Other studies of children revolve around physiological measurements of pressure while on HFNC therapy. Two studies measured nasopharyngeal pressure, one oesophageal pressure (as a proxy for pleural pressure), and the other measured both pharyngeal and oesophageal pressures. All studies determined that increasing flow resulted in increased pressure, and that this likely improved the effort of breathing. Milesi et al concluded that flows ≥2 L/kg/min were associated with a mean pharyngeal pressure of ≥4 cmH$_2$O. Arora et al determined that there was a linear relationship between increasing flow (1–6 L/min) and nasopharyngeal pressure (NP) in both open and closed mouth states. A mean NP of 3.4 cmH$_2$O showed clinical improvement, with a pressure maximum of 5 cmH$_2$O. Rubin et al measured oesophageal pressure as a reflection of pleural pressure and hence an objective measurement of breathing effort (as opposed to subjective scoring systems). In this study, effort of breathing decreased 25% when the flow rate was increased from 2 to 8 L/min.

The majority of paediatric studies focus on a specific population group: infants with bronchiolitis. This is likely due to the fact that bronchiolitis is the leading cause of non-elective hospitalisation worldwide, and that this population is a homogenous group. Most studies took place in an ICU. This may be because this level of respiratory support has
normally been administered in a dedicated ICU setting, whether paediatric or mixed population ICUs. However it may be possible to deliver this level of support outside the PICU, in lower (ward) environments.

Three studies examined HFNC therapy in the ward environment\textsuperscript{143,149,150} Another study commenced support in the emergency department, and then transferred patients to the PICU\textsuperscript{151} and another assessed HFNC therapy used in the retrieval of paediatric patients.\textsuperscript{152} In two of the three ward studies, no escalation to further respiratory support occurred.\textsuperscript{143,149} Only one study reported transfer of patients to the PICU, where out of 5 patients transferred (25 patients in study), 1 was intubated and the remaining 4 required NIV.\textsuperscript{150} This study also showed an economic benefit to managing patients on the ward, when compared to historical data for infants with bronchiolitis admitted to the PICU. The percentage of costs derived from these patients being cared for in the PICU (over the previous 5 seasons) was 12.6%, and decreased to 4.8% with the implementation of HFNC therapy in this hospital's ward environment.\textsuperscript{150} However, the study acknowledged that further studies are required to completely determine the cost saving for this institution.

Two case series studies of HFNC therapy use in paediatrics have been reported. One details HFNC therapy used in a child with inhalation burns and a post-extubation stridor. In this scenario, HFNC therapy successfully prevented urgent intubation, with the patient maintained comfortably over a number of days.\textsuperscript{153} The second case series reported three cases of air leak syndrome (pneumothorax and pneumomediastinum) which occurred during the use of HFNC therapy in children with bronchiolitis, pneumonia and post-extubation (for subdural haematoma).\textsuperscript{154} However, the authors concluded that there was no way to determine cause and effect in these three cases. Certainly, infants with bronchiolitis developing spontaneous pneumothorax has been documented, and in one case series this was successfully treated with HFNC therapy.\textsuperscript{155} So while it remains a potential adverse event, no other reports exist to date of spontaneous air leak syndrome occurring in any studies presented here, or assessed in various systematic reviews.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Participants (n=)</th>
<th>Comparator/Intervention</th>
<th>Outcome</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Byerley&lt;sup&gt;153&lt;/sup&gt;</td>
<td>2006</td>
<td>Case study</td>
<td>n=1, 12 month old burn patient with inhalation injury and post-extubation stridor, in PICU</td>
<td>HFNC</td>
<td>Prevented urgent intubation, comfort increased as respiratory distress decreased.</td>
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<tr>
<td>McGinley&lt;sup&gt;156&lt;/sup&gt;</td>
<td>2009</td>
<td>Prospective observational study</td>
<td>n=12 children (10±1 years) with obstructive sleep apnoea. In Sleep Clinic</td>
<td>Nasal insufflation at flow 20 L/min</td>
<td>Improved oxygenation and decreased arousal led to decreased occurrence of obstructive apnoea.</td>
<td>Comparable therapy to CPAP.</td>
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<tr>
<td>Spentzas&lt;sup&gt;80&lt;/sup&gt;</td>
<td>2009</td>
<td>Prospective observational study</td>
<td>n=46, newborn to 12 years, median age 2.8 years, in PICU</td>
<td>Received NC or mask before switch to HFNC. Flow rates 8–12 L/min for infants and 20–30 L/min for children. Np measured.</td>
<td>Clinical indicators including RDS, COMFORT scale, and SpO₂ improved on HFNC within 60–90 mins. Average positive airway pressure 4±1.99 cmH₂O.</td>
<td>Pressure increased with flow, and an association with weight. Heterogeneous population. No adverse events.</td>
</tr>
<tr>
<td>McKiernan&lt;sup&gt;145&lt;/sup&gt;</td>
<td>2010</td>
<td>Retrospective observational study</td>
<td>n=115 infants &lt;2 years with bronchiolitis (median age 2 and 3 months respectively), in PICU</td>
<td>Pre-HFNC n=57, post-HFNC n=58, flow rate 7 and 8 L/min.</td>
<td>Reduced intubation after HFNC implemented (14% absolute risk reduction). No significant decrease of RR to HFNC within 1 hour predicted failure.</td>
<td>No adverse events in HFNC group.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Type</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcome</td>
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<tr>
<td>Schibler&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2011</td>
<td>Retrospective observational study</td>
<td>n=298 infants &lt;2 years, in PICU</td>
<td>HFNC to max flow of 8 L/min</td>
<td>19% required NIV and 12% required intubation overall. In bronchiolitis patients only 4% required escalation of therapy. Bronchiolitis responders identified by 20% reduction in HR and RR within 90 mins of therapy commencing. No adverse events. Overall there was a decrease in intubation from 37% to 7% over study period.</td>
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<tr>
<td>Abboud&lt;sup&gt;147&lt;/sup&gt;</td>
<td>2012</td>
<td>Retrospective observational study</td>
<td>n=113, age ≤12 months with bronchiolitis, in PICU</td>
<td>HFNC (flow 3–8 L/min)</td>
<td>n=92 responders, n=21 non-responders. Non-responders did not change their RR and had higher PRISM scores. Persistence of desaturations was strongly associated with HFNC failure. RR was predictive, responders decreased their RR significantly (non-responders did not change their RR and had lower RR to begin with and higher PCO&lt;sub&gt;2&lt;/sub&gt;, possibly due to inability to compensate.</td>
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<tr>
<td>Arora&lt;sup&gt;148&lt;/sup&gt;</td>
<td>2012</td>
<td>Prospective observational study</td>
<td>n=25, mean age 78.1 days, infants with bronchiolitis in PED</td>
<td>HFNC commenced 1 L/min to max of 8 L/min. Np measured</td>
<td>Linear increase in pressure as flow increased. Average 0.45 cmH&lt;sub&gt;2&lt;/sub&gt;O pressure increase with each 1 L/min flow increase. Weight and gender not associated with pressure generated. Patients transferred to ward and PICU.</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Population</td>
<td>Interventions</td>
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<tr>
<td>Hilliard</td>
<td>2012</td>
<td>Prospective, randomised, open pilot study</td>
<td>n=19 infants (median age 3.0 months) with bronchiolitis, in ward</td>
<td>HFNC (n=11) vs head box (n=8)</td>
<td>Median SpO2 higher in HFNC group at 8 and 12 hours. No adverse events, no admission to PICU or escalation of respiratory support.</td>
<td></td>
</tr>
<tr>
<td>Wing</td>
<td>2012</td>
<td>Retrospective observational study</td>
<td>n=848. Three cohorts, pre-HFNC (mean age 4.6 years), pre-guidelines (mean age 4.1 years) and post-guidelines (mean age 4.8 years). In PED then admitted to PICU</td>
<td>HFNC</td>
<td>Post guideline implementation there was a 50% relative risk reduction in intubations, mostly accounted for in the PED. Heterogeneous population with acute respiratory insufficiency.</td>
<td></td>
</tr>
<tr>
<td>Bressan</td>
<td>2013</td>
<td>Prospective observational pilot study</td>
<td>n=27 infants (median age 1.3 months) with mod–severe bronchiolitis, in ward</td>
<td>HFNC at flow rate = weight + 1 (L/min)</td>
<td>RR decreased by 13–20 breaths per minute in the first 3 hours of HFNC. No adverse events, no escalation of therapy.</td>
<td></td>
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<tr>
<td>Brink</td>
<td>2013</td>
<td>Prospective observational study</td>
<td>n=109, children (median age 6 and 5 months respectively) requiring respiratory support, in PICU</td>
<td>HFNC at 2 L/kg/min (n=72) vs NP-CPAP (n=37)</td>
<td>Escalation of therapy could be predicted by failure of HR and RR response, and FiO2 ≥0.5 within 2 hours. 26% of HFNC required escalation of therapy compared to 18% on NP-CPAP. HFNC had a shorter therapy time compared to NP-CPAP. No pneumothorax in the HFNC group, 2 in the NP-CPAP. Reduced sedation use in HFNC group.</td>
<td></td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Study Design</td>
<td>Sample Characteristics</td>
<td>Equipment</td>
<td>Key Findings</td>
<td>Notes</td>
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<tr>
<td>Kelly</td>
<td>2013</td>
<td>Retrospective observational study</td>
<td>n=498 infants &lt;2 years presenting with respiratory distress, in two PEDs</td>
<td>HFNC</td>
<td>8% required intubation. Initial RR &gt;90&lt;sup&gt;th&lt;/sup&gt; percentile for age, venous PCO&lt;sub&gt;2&lt;/sub&gt; &gt;50mmHg and pH &lt;7.3 increased risk of HFNC failure.</td>
<td>Prematurity was not predictive of failure.</td>
</tr>
<tr>
<td>Milesi</td>
<td>2013</td>
<td>Prospective observational study</td>
<td>n=21, &lt;6 months with RSV bronchiolitis, in PICU</td>
<td>HFNC at flow 1, 4, 6, 7 L/min, Pp and Op measured simultaneously</td>
<td>Flow ≥2 L/kg/min associated with mean PP ≥4 cmH&lt;sub&gt;2&lt;/sub&gt;O.</td>
<td>Homogenous population. No adverse events.</td>
</tr>
<tr>
<td>Gonzales-Martinez</td>
<td>2013</td>
<td>Prospective observational study</td>
<td>n=25, infants &lt;18 months (median age 2.0 months) with bronchiolitis, in ward</td>
<td>HFNC</td>
<td>Significant reduction in HR, RR and scale of severity after initiation of HFNC.</td>
<td>No adverse events. 5 admitted to PICU (80% reduction on historical data, and substantial economic saving), 1 intubated, 4 NIV.</td>
</tr>
<tr>
<td>Hedge</td>
<td>2013</td>
<td>Case study</td>
<td>n=3, 2 month old with bronchiolitis and flow 6 L/min (PICU), 16 year old with cerebral palsy with flows at 4, 8, 15, 20 L/min (HDU to PICU), 22 month old with subdural haematoma with 6 L/min flow post-extubation (PICU)</td>
<td>HFNC and insufflation used</td>
<td>All developed air leak syndrome.</td>
<td>Exact cause and effect could not be established.</td>
</tr>
<tr>
<td>Rubin</td>
<td>2014</td>
<td>Prospective observational study</td>
<td>N=25, children &lt;18 years, median age 6.5 months. In PICU and cardiothoracic ICU</td>
<td>HFNC at 2–8 L/min and compared to CPAP 4–5 cmH&lt;sub&gt;2&lt;/sub&gt;O (while intubated) and NC. Op measured</td>
<td>Increased flow increased pressure. Decreased RR with increased flow.</td>
<td>Not powered for CPAP comparison. Heterogeneous population. No adverse events.</td>
</tr>
</tbody>
</table>
Schlapbach\textsuperscript{152} 2014  Retrospective observational study  n=793 infants <2 years, transported by specialised paediatric retrieval team (2005–2012)  Pre- and post-HFNC introduction to retrieval  Significant reduction in intubation by retrieval team.  No patient retrieved on HFNC needed intubating during transport or developed pneumothorax or cardiac arrest.  

HFNC = high flow nasal cannula; NC = nasal cannula; CPAP = continuous positive airway pressure; NP-CPAP = nasopharyngeal CPAP; NIV = non-invasive ventilation; RR = respiratory rate; HR = heart rate; RDS = respiratory distress syndrome; Np = nasopharyngeal pressure; Op = oesophageal pressure; Pp = pharyngeal pressure; PICU = paediatric intensive care unit; PED = paediatric emergency department
3.6 Adverse events

Reports of adverse events appear to be limited in the studies published to date. Within the pre-term/neonatal population, nasal mucosal trauma has been associated with HFNC that is unheated and not humidified. One case report exists of an incidence of scalp emphysema and pneumocephalus in a neonate. In infants and children, most studies report no adverse events. However in a recent prospective study, two patients had abdominal distension and one a mucosal injury during HFNC therapy. These cases are relatively infrequent, and causation is unclear. In adult studies there have been no reports of adverse events such as pneumothorax/air leak syndrome, abdominal distension or nasal trauma. However, ongoing concern remains over the potential for adverse events from HFNC therapy, thus further research is required, as is monitoring of outcomes where HFNC therapy has become part of practice. This may be addressed with large RCTs.

3.7 Feeding method during HFNC therapy

During HFNC therapy delivery, the mode of feeding used may also be of interest. Generally, when there is severe respiratory distress, patients are hydrated either via intravenous fluid infusion or entrally via nasogastric tubes. However, as a patient's respiratory status improves, the potential exists to transition to oral feeding. This is valuable, especially in the pre-term, neonatal and infant populations due to comfort derived from breast/oral feeding, and the associated establishment of suck/swallow reflex especially with pre-term neonates. However, within the current literature, feeding mode while receiving HFNC is seldom reported. In a recent survey (2013) of neonatal ICUs in the United Kingdom, 46% of respondents found it easier to bottle/cup feed infants on HFNC, compared to nasal CPAP. Three paediatric studies report the use of oral feeding while on HFNC, all with no apparent adverse events such as aspiration. For clinicians, it is likely that the argument surrounding whether to orally feed stems from the amount of flow delivered and the perceived inability of the neonate/infant to coordinate a suck-swallow reflex with higher flows. However, an equally likely explanation may be that a neonate/infant's work of breathing may reduce their ability to suck/swallow effectively in these situations, and as their respiratory function improves, they are at no greater risk of aspiration from orally feeding on high flows than at any other time.

The importance of resolving this dilemma lies in the comfort that breast/bottle feeding can deliver, as well as the impact on hospital length of stay. Close clinical observation would
be needed to ensure the neonate/infant is not compromised while feeding, and determinations made in the first instance as to the neonate/infant's ability to manage oral feeds and work of breathing. Usual practice is to ensure infants are established on oral feeds prior to hospital discharge, so commencing oral feeds while still on HFNC therapy may assist with decreasing hospital length of stay. However, although it lies beyond the scope of this thesis, further robust research is needed to determine if there is higher risk of aspiration during oral feeding, and what the benefits are, compared to other modes such as enteral or intravenous feeding.

3.8 Practice creep
Scope creep is a term often used in project management and refers to uncontrolled changes or continuous growth in a project's scope.\(^{159}\) Within medicine and nursing, a situation that moves beyond traditional boundaries can be labelled similarly as 'practice creep'.\(^{160,161}\) This concept can be applied to the rapid uptake of HFNC therapy within clinical practice, not only in ICUs but also other acute care environments.

The conundrum with practice creep in this context is that it is based on collections of studies that still have limited power to determine the effectiveness, efficacy and safety of HFNC across the whole patient age range. Yet, as it has been perceived in clinical practice to be a useful modality of respiratory support, it is becoming more widely used without the rigour of a well-constructed RCT underpinning its process and limits.

3.9 Conclusion
This chapter described the mechanism of action of HFNC and presented the studies that have been undertaken across the spectrum of patient ages. The consistent message is that large RCTs are needed to underpin the initial findings that all these studies have reported. Those findings are that HFNC therapy may offer an alternative mode of treatment for a range of patients with respiratory compromise; potentially offer a degree of PAP, which may help to keep obstructed airways open and provide respiratory support; improve work of breathing, be more comfortable and better tolerated than face masks; and may prove to be a cost-effective treatment, reducing hospital length of stay, PICU admission rates and the need for intubation. With the growing evidence of practice creep in the ward environments, it may also have a safe application outside of the ICU, where responders to therapy can be identified early, by predefined markers denoting escalation of therapy.
3.10 Publication

The following publication presents the PICU experience at the Mater Children’s Hospital, Brisbane, and the clinical use of HFNC therapy in managing patients with respiratory compromise. HFNC therapy has been in use since 2005, and in-unit data illustrates dramatically reduced intubation rates for infants presenting with bronchiolitis. Within this unit, HFNC therapy has become the first line of support for any patient with respiratory difficulties. In consultation with clinical experts in PICU and the advisory team, three patients were chosen with moderate to severe work of breathing with differing and distinct underlying pathophysiologies. Cases were examined from each three categories over a 2 year period. Presented as a case series, three patients are profiled and their course of treatment and management during their PICU stay presented. The range of patients encompasses physiological conditions affecting small airways (bronchiolitis), large airways (asthma), and cardiopulmonary interplay (cardiomyopathy).
Case study
A series of paediatric high flow nasal cannula therapy

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\textbf{Abstract}

\textbf{Introduction:} High flow nasal cannula is an emerging treatment option in Paediatric Intensive Care Units for paediatric patients in acute respiratory distress. Yet there is a paucity of literature describing its clinical application in various presenting pathophysiology.

\textbf{Aim:} To describe three cases with differing underlying pathophysiology and their response to high flow nasal cannula oxygen therapy.

\textbf{Method:} Patients admitted to the Paediatric Intensive Care Unit with bronchiolitis, asthma and cardiomyopathy, and treated with high flow nasal cannula therapy were searched in the Paediatric Intensive Care database. The most representative cases were chosen to review.

\textbf{Results:} One infant and two children were reviewed. All were commenced on high flow nasal cannula therapy in the Paediatric Intensive Care Unit and all demonstrated an improvement in their work of breathing. There was also a substantial improvement in their haemodynamic status. No patient required escalation to other forms of respiratory therapy.

\textbf{Conclusion:} High flow nasal cannula therapy is a viable treatment option for a range of patients presenting to the Paediatric Intensive Care Unit with acute respiratory distress. More invasive methods of respiratory support may be avoided by the use of high flow nasal cannula therapy.

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\section*{Introduction}

Respiratory illness is the leading cause of admission of infants, children and adolescents to Australian hospitals each year.\textsuperscript{1} Bronchiolitis, asthma and pneumonia comprise the majority of non-elective admissions due to acute respiratory insufficiency (ARI) or acute respiratory failure (ARF) to Paediatric Intensive Care Units (PICUs) across Australian and New Zealand hospitals (25% of all admissions in 2011).\textsuperscript{2} Patients experiencing ARI due to cardiac failure represent a smaller but no less important group.

For many of these patients, management with mechanical ventilation through an endotracheal tube (ETT) is well established and often lifesaving. More recently many have been managed non-invasively (NIV) using continuous positive airway pressure (CPAP) with nasal or facial masks/prongs to avoid intubation.\textsuperscript{3,4} Both methods have clinical limitations. Intubation and mechanical ventilation can include complications such as ventilator associated pneumonia (VAP), ventilator induced lung injury (VILI), airway injury due to ETT placement and complications arising from sedation. For the cardiac patient, intubation and mechanical ventilation can further compromise left ventricular function especially in the presence of cardiac failure.\textsuperscript{5} The limitations of NIV include maintaining an adequate seal to the face/nasal area, difficulty in keeping the apparatus on and potential for septal erosion with nasal prongs.\textsuperscript{6,7}

Heated and humidified high flow nasal cannula (HFNC) oxygen therapy is an emerging treatment option for respiratory support in patients of all ages. HFNC therapy allows delivery of high inspired gas flows of 2–70 L/min, with or without blended air/oxygen mix, is heated and humidified and is delivered via nasal cannula. The humidity and warmth achieved with HFNC improves mucociliary clearance and this facilitates the removal of secretions.\textsuperscript{8–11} Additionaly the bronchocstriction reflex triggered by cold, dry air is diminished.\textsuperscript{7} HFNC has been used successfully as an alternative to nasal CPAP in the preterm infant population to manage apnoea of prematurity and ARF.\textsuperscript{8–11} It has been reported in preterm infants that HFNC provides end-expiratory pressures of up to 6 cm H\textsubscript{2}O using flow rates of up to 8 L/min.\textsuperscript{8,12} A recent study by Spentzas and colleagues,\textsuperscript{13} demonstrated that in older...
children HFNC provides an average positive expiratory pressure of 4.0 ± 1.99 cm H₂O. A physiologic study by Milesi and colleagues has shown that a flow rate of ≥2 L/kg/min improves the breathing pattern and WOB of infants with bronchiolitis. While the CPAP effect is yet to be fully understood it is hypothesised that the high flow rates flush the anatomical dead space of the nasopharyngeal cavity, resulting in improved alveolar ventilation as well as washing out carbon dioxide which has an effect on reducing apnoeas secondary to hypercapnia.

There is increasing evidence in paediatric populations that HFNC is an effective treatment for ARI and ARF and is associated with a decreased need for intubation and ventilation Another benefit of HFNC over NIV systems is an overall increase in patient comfort levels and tolerance of the device. This may translate into a reduced need for sedation agents. Furthermore there is an overall decrease in both respiratory rate and WOB with this apparatus as well as a reduced incidence of nasostralia.

While there is increasing uptake of the use of HFNC in the clinical environment, some reviewers have urged caution in relation to widespread use. Yet in the absence of higher levels of evidence to guide clinical decision-making it becomes important to report on the use of HFNC in the clinical setting to facilitate understanding of this therapy as an supplement of care. Case studies can be a valuable resource and educational resource and when reported as such around a particular aspect of care, can provide new insights and stimulate research in response to knowledge gaps. Following an extensive literature search the use of HFNC as a treatment for respiratory compromise arising from varied pathophysiologies in paediatric patients has not been previously reported.

This paper aims to report the use of HFNC therapy within a PICU on three patients with moderate to severe WOB and differing underlying pathophysiology. We provide tertiary care in a metropolitan paediatric hospital. In 2011, 17,618 patients were admitted to our children’s hospital with over 1200 patients to our PICU. Of the PICU admissions, 53% were non-elective admissions of which 28% were comprised of respiratory or cardiac failure patients. HFNC therapy was used in 30% of all our patients to manage their WOB and was day 4 of her illness.

Case one

A 3-month-old (age adjusted) girl, born at 26 weeks gestation and weighing 3 kg was admitted to PICU via the emergency department (ED) with Respiratory Syncytial Virus (RSV) positive bronchiolitis. On presentation she had severe to moderate WOB with an increased respiratory rate (RR) and heart rate (HR). This was day 4 of her illness.

She had previously required intubation at birth for increased WOB and was extubated to CPAP at 10 h of age. CPAP continued for six weeks prior to discharge home.

In PICU she was commenced on HFNC therapy at 6 L/min (2 L/kg/min) and FiO₂ adjusted to maintain oxygen saturations >94%. The flow was dialed up slowly over a couple of minutes.

Within the first hour she responded to treatment as evidenced by a significant decrease in her HR and RR from 170 bpm and 70 bpm to 149 bpm and 51 bpm respectively (Fig. 1). While she had paracetamol prescribed as needed, she did not require any pharmacological sedation (e.g. chloral hydrate) to assist tolerance of the HFNC device. Feeding was managed via a nasogastric tube at a rate specified by the dietitian to meet her caloric needs. Within 24 h her WOB had improved to mild, and HFNC therapy was ceased by turning the flow off completely. During her admission there was no need to progress to other forms of ventilation such as mask/nasal NIV or invasive ventilation. She was discharged from PICU after 37 h to the ward on low flow nasal cannula oxygen of 0.5 L/min. Four days later she was discharged home.

Case two

A 3-year-old girl weighing 17.5 kg was admitted to the PICU via ED with viral (human metapneumovirus) induced exacerbation of asthma. She had an increased WOB that was unresponsive to salbutamol metered doses (200 mg/dose as bursts of 6 via spacer) in the ED. She had been given a magnesium load of 1.8 mmol intravenously (IV) in the ED and commenced on Cefotaxime 900 mg, eighth hourly (q8), IV. Steroids (hydrocortisone) were also commenced in the ED to address the inflammatory process, in addition to the Cefotaxime to cover a suspected pneumonia.

On arrival to PICU she was speaking in short sentences with little air movement on auscultation and she had severe intercostal recession and a tracheal tug. Salbutamol was continued in the PICU, initially as a metered aerosol 200 mg/dose (4 episodes over 1.5 h via a spacer) then as 5 mg hourly via nebuliser. HFNC therapy was commenced at 2 L/kg/min equating to 351 L/min on arrival to PICU.

Within the first hour of application of HFNC her HR and RR dropped considerably from 157 bpm and 56 bpm to 146 bpm and 48 bpm respectively and continued to improve (Fig. 2). As her WOB improved she was able to speak in longer sentences. After 38 h of HFNC therapy she was able to be weaned to low flow nasal cannula oxygen therapy. Weaning was achieved by reducing the FiO₂ to .30 (maintaining saturations >92%) and turning the flow off.

She was transferred to the ward with a faint bibasal wheeze, continuing salbutamol nebulisers (as required) and low flow nasal cannula oxygen requirement to maintain SaO₂ >92%. Her PICU stay was 1.75 days and she was discharged to home three days later.

Case three

A 2-year-old boy weighing 12 kg was admitted to the PICU via ED with a history of cough, lethargy and decreased oral intake. After examination it was determined that he was in cardiac failure due to...
When reviewing our case series, we describe three cases with differing presentations and the effect of HFNC treatment on RR, HR and WOB. Our previous practice typically used NIV for respiratory support in the presence of ARI or ARF due to bronchiolitis, asthma and for left ventricular afterload reduction in cardiac failure. Since HFNC is delivering a similar type of respiratory support to NIV,13 we describe cases where this type of support has had an apparent impact on the improvement of the patient.

Case one represents a typical infant presenting with bronchiolitis often seen as a seasonal presentation in the winter months. In this case there was a positive response to the HFNC therapy within the first hour as evidenced by a decrease in HR and RR and no subsequent need to progress to any other form of respiratory support. This is supported by findings from a previous study which showed that those who responded to HFNC therapy within the first 90 min by a decrease in HR and RR were unlikely to progress to any other form of respiratory support.11–12 Since commencing use of the HFNC system within our unit to treat infants with bronchiolitis we have decreased our PICU length of stay for these patients by 24 h as compared to other centres in Australia.2 In reviewing our unit data for intubation rates in bronchiolitic infants, we observed a decrease from 8% in 2011 to 3% in 2012, with both rates being much lower than any other PICU in Australia and New Zealand. By avoiding intubation in these patients the risks associated with invasive ventilation, such as VAP, VILI and issues surrounding the use of sedation (such as neuromuscular wasting and withdrawal) are also avoided.

In Case two there was a drop in the HR and RR within the first 2 h after HFNC treatment commenced. The response is unlikely to be due to the effect of steroids as only one dose had been given prior to HFNC commencing. Likewise, Salbutamol had been given via a spacer/metered aerosol combination in ED and PICU with little effect on decreasing HR, RR or WOB. Given the dose response time for Cefotaxime is a number of hours this would not have had an effect at this stage either. We suggest that the improvement in HR and RR coincides with the commencement of HFNC therapy. This effect is also in concordance with an earlier paediatric study.18 In an adult case report by Boyer and colleagues,24 they also described a similar treatment effect of improvement in HR and RR with the application of HFNC therapy for an adult patient in respiratory distress with underlying pulmonary fibrosis.

Case three represents a challenge in balancing cardiac function and support with respiratory function. In a healthy heart, the influence of spontaneous respiration on left ventricular (LV) function is relatively unimportant. However in patients with diminished myocardial function, such as dilated cardiomyopathy, a change in intrathoracic pressure due to positive pressure ventilation (via endotracheal tube), can cause an acute decrease in right ventricular (RV) preload and further decrease cardiac output, especially in an under filled heart. The application though of short term CPAP via NIV in these patients can reduce both RV and LV preload, but the adverse effects of invasive ventilation.24 This can give the benefits of improved work of breathing and oxygenation (by mitigating pulmonary oedema) and improved cardiac output by decreasing LV afterload.25 The potential CPAP induced reduction in cardiac volume could contribute to reductions in atrial stretch, and help improve overall cardiac function.24

Within the adult population HFNC is becoming a popular treatment to manage patients with ARI due to cardiac failure.25 HFNC is better tolerated over a wide age range when compared to NIV.13,18 This can be of benefit in the paediatric population with cardiac failure as there is less need for sedation in order to maintain placement of an NIV system. As HFNC delivers a similar degree of CPAP the beneficial effects to cardiac function are maintained without the negative effects of using other pharmacotherapy to keep NIV in situ.

In the cases presented our clinical practice in relation to HFNC is to use 2 L/kg/min of flow and adjust FiO2 to oxygen saturations.

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**Discussion**

The aim of this case series was to describe three cases with differing presentations and the effect of HFNC treatment on RR, HR and WOB. Our previous practice typically used NIV for respiratory support in the presence of ARI or ARF due to bronchiolitis, asthma and for left ventricular afterload reduction in cardiac failure. Since HFNC is delivering a similar type of respiratory support to NIV,13 we describe cases where this type of support has had an apparent impact on the improvement of the patient.

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In the cases presented our clinical practice in relation to HFNC is to use 2 L/kg/min of flow and adjust FiO2 to oxygen saturations.
We determined the level of flow from our own clinical research and clinical observation of patients commenced on HFNC therapy. Our practice changed in mid-2011 to accommodate delivering 2 L/kg/min flow to all our patients as prior to that we were limited in our flow delivery by the apparatus used. Importantly there were no adverse effects of HFNC treatment, such as pneumothorax/air leak syndrome, nasal trauma or abdominal overdistention in any of the three cases reported.

Limitations

The physiological effect of HFNC therapy is yet to be fully examined in paediatric patients in any of the underlying disease processes presented. We have only hypothesised, from adult and neonatal studies published to date, the effect that HFNC may be having on these patients. Case reports and series have limited external validity however in the absence of higher level research evidence this provides support for the use of HFNC treatment in paediatrics.

Conclusion

HFNC systems are increasingly being used in intensive care settings and across a range of patient age groups and conditions. These case reports highlight a range of conditions in paediatric patients where HFNC therapy may be beneficial. Our case series suggests that HFNC therapy is an effective treatment for patients with these three diagnoses and may prevent invasive ventilation in a variety of clinical scenarios, improve recovery times and shorten length of stay in the PICU. However, as with all emergent therapies, further investigation particularly randomised clinical trials are required to strengthen the evidence for its use as a recognised and effective mode of non-invasive respiratory support.

Author contributions

Sara Mayfield: Ms Mayfield conceived the case series, identified the cases, acquired the consent and data, drafted the initial manuscript and approved the final manuscript as submitted.

Jacqui Jauncey-Cooke: Ms Jauncey-Cooke assisted with the presentation of the data, contributed critical revisions of the draft, and approved the final manuscript as submitted.

Fiona Bogossian: A/Prof Bogossian supported Ms Mayfield in conceiving the case series, implementation and contributed critical revisions to the manuscript and approved the final manuscript as submitted.

Conflict of interest

The authors have no conflicts of interest to disclose.

References


Chapter 4: Cochrane Review

4.1 Introduction

To date, this thesis has examined bronchiolitis, its natural history, sequelae, health service response and treatment options. It has also explored the use of HFNC therapy, an emergent treatment option, across the patient age span. This chapter will provide a systematic review of the literature regarding HFNC use within the paediatric population.

In 1995, Guyatt et al\textsuperscript{162} proposed a hierarchy of evidence for assessing study designs and the strength of evidence generated, in order to determine the applicability of findings to clinical practice. Traditionally systematic reviews of RCTs and meta-analysis form the pinnacle of the pyramid.\textsuperscript{163} Then follow RCTs, other controlled clinical trials, observational studies, and finally, lower evidence comprising case studies, anecdote and opinion (Figure 4.1).

![Image of traditional hierarchy for assessing evidence]

Figure 4.1 – The traditional hierarchy for assessing evidence

The gold standard for systematic reviews is The Cochrane Collaboration. Archie Cochrane established the Cochrane Database of Systematic Reviews in the 1980s in an effort to
provide a central hub for synthesising evidence from multiple individual trials. The Cochrane Collaboration is organised into review groups, based on speciality fields, disease or organ classification.\textsuperscript{164} In embarking on a review, the first step is identifying which group to contact. From there, a title registration form is completed and, if registration is successful, a protocol is developed, providing both the framework for identifying eligible studies and the statistical analysis required to assess the evidence. This then leads onto a review (Figure 4.2). Many small studies, such as those in paediatrics, lack the sample size and hence power to inform clinical practice changes independently. However, by pooling data from homogenous studies into a meta-analysis, statistical significance may be found supporting either a positive or negative impact of a treatment, which then informs clinical practice.

The title registration form is a comprehensive outline of what the protocol will entail. It includes a title, based on standard Cochrane format (replicates PICO – Population, Intervention/Indicator, Comparator/Control, Outcome), motivation for the proposed review, and description of the proposal. For a title to progress onto a protocol, each Cochrane group requires certain elements to be included in the team undertaking the review, such as content expert, methodologist or statistician and experience of co-authors in the Cochrane process. It is essential to refer to The Cochrane Collaboration handbook, as this guides authors in the conduct of a systematic review and becomes the 'bible' to follow to ensure success in producing the highest quality work possible.\textsuperscript{165}

Once the title is registered, work can begin on the protocol and follows the structure outlined in The Cochrane Collaboration handbook. All content is rigorously evaluated by each of the Cochrane Group's Editorial team. Once all elements are finalised and approved by the editorial team, the protocol is then published.
The protocol gives guidance and outlines intention for the review and subsequent updates. For a review into the use of HFNC and bronchiolitis, the Acute Respiratory Infections Group was approached to determine whether a proposed title, 'High flow nasal cannula therapy for respiratory support of infants with bronchiolitis' could be registered. However, the group advised that another team had already registered a title. Subsequently, it was decided to broaden the review to include all children, regardless of underlying pathophysiology, treated with HFNC.

The Cochrane Anaesthesia Review Group (CARG) was therefore approached, a title was registered, and subsequently a protocol and review were undertaken with CARG’s guidance and supervision. However, CARG do not review studies involving neonates, who comprise pre-term (<37 completed weeks gestation) to one month post-term (44 weeks), and because the group of infants from term to one month are disproportionally represented in PICUs, including them in any review of HFNC is critical. Therefore another title was registered, and subsequent protocol and review (pending) were undertaken with the Neonatal Review Group.

When conducting the review, the processes outlined in the protocol are essential and must be adhered to, and if not, justification must be forthcoming. For the review conducted with the CARG, following input from their editorial team, any studies relating to children with bronchiolitis were removed as another group were undertaking this study and it was thought to be an unnecessary replication.
The CARG staff undertook the literature search (conducted by Karen Hovhannisyan) and the 900 results forwarded on. The results were scoured for applicability to the review, removing all abstracts that did not meet the outlined criteria. After this stage, the full text of remaining published studies were obtained and vigorously analysed for applicability and inclusion in the review. The CARG editorial team intensely scrutinise the reviews, ensuring the high quality of the resultant publication.

The Neonatal Review Group employs the same high standard when conducting their reviews, and the same rigour was applied to their protocol, and is expected to be applied to the review when undertaken (late 2014/early 2015).

Finally, the reviews are updated every two years, ensuring that clinicians worldwide have the most robust statistical summation of all available evidence on current advances in this territory.

4.2 Publication – Cochrane Collaboration Anaesthesia Review Group review
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High-flow nasal cannula therapy for respiratory support in children

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Editorial group: Cochrane Anaesthesia Group.


Review content assessed as up-to-date: 1 April 2013.


ABSTRACT

Background

Respiratory support is a central component of the management of critically ill children. It can be delivered invasively via an endotracheal tube or non-invasively via face mask, nasal mask, nasal cannula or oxygen hood/tent. Invasive ventilation can be damaging to the lungs, and the tendency to use non-invasive forms is growing. However, non-invasive delivery is often poorly tolerated by children. High-flow nasal cannula (HFNC) oxygen delivery is a relatively new therapy that shows the potential to reduce the need for intubation and be better tolerated by children than other non-invasive forms of support. HFNC therapy differs from other non-invasive forms of treatment in that it delivers heated, humidified and blended air/oxygen via nasal cannula at rates ≥ 2 L/kg/min. This allows the user to deliver high concentrations of oxygen and to potentially deliver continuous distending pressure; this treatment often is better tolerated by the child.

Objectives

To determine whether HFNC therapy is more effective than other forms of non-invasive therapy in paediatric patients who require respiratory support.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 4); MEDLINE via PubMed (January 1966 to April 2013); EMBASE (January 1980 to April 2013); CINAHL (1982 to April 2013); and LILACS (1982 to April 2013). Abstracts from conference proceedings, theses and dissertations and bibliographical references to relevant studies were also searched. We applied no restriction on language.

Selection criteria

We planned to included randomized controlled trials (RCTs) and quasi-randomized trials comparing HFNC therapy with other forms of non-invasive respiratory support for children. Non-invasive support encompassed cot, hood or tent oxygen; low-flow nasal cannulae (flow rates ≤ 2 L/min); and continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) delivered via facial or nasal mask/cannula. Treatment failure was defined by the need for additional respiratory support. We excluded children with a diagnosis of bronchiolitis.
Data collection and analysis
Two review authors independently assessed all studies for selection and data extraction. We used standard methodological procedures expected by The Cochrane Collaboration.

Main results
Our search yielded 922 records. A total of 109 relevant records were retrieved with reference to our search criteria. After duplicates and irrelevant studies were removed, 69 studies were further scrutinized. Of these, 11 studies involved children. No study matched our inclusion criteria.

Authors’ conclusions
Based on the results of this review, no evidence is available to allow determination of the safety or effectiveness of HFNC as a form of respiratory support in children.

PLAIN LANGUAGE SUMMARY
High-flow nasal cannula therapy for support of breathing in children
We reviewed evidence on the effectiveness of high-flow nasal cannula (HFNC) therapy in supporting children’s breathing. We found 11 studies in children.

Background
HFNC therapy delivers a mixture of air and oxygen via tubing that sits just inside the nostrils. For children hospitalized with breathing difficulties caused by conditions such as pneumonia or trauma or after surgery, HFNC therapy may help to support their breathing. This may reduce the need for other forms of breathing support such as life support. HFNC therapy can be used within the hospital ward setting, the emergency department or the intensive care unit. This Cochrane review is important because it assesses available evidence on the safety and effectiveness of HFNC compared with other forms of respiratory support, to help inform clinicians caring for children with breathing difficulties.

Search date
We searched medical databases from the 1950s until April 2013.

Study characteristics
We included studies on children from four weeks to 16 years of age. We searched for randomized controlled trials; however we excluded studies involving infants with bronchiolitis (a respiratory illness affecting infants that typically mimics a common cold) because children with this condition are included in another Cochrane review.

Results
We found 11 studies involving children; however none matched our criteria.

Conclusion
It is important that good-quality studies are completed to identify indications as to the use and effectiveness of HFNC therapy in supporting the breathing of ill children.
BACKGROUND

Description of the condition

Respiratory support is central to the care of critically ill children. Support may be needed because of underlying disease processes such as respiratory infection or pneumonia, neuromuscular disorders, cardiac conditions or cardiac failure, and as the result of other mechanisms such as upper airway obstruction, trauma and injury or post-surgical interventions. Respiratory support can be delivered non-invasively in the form of oxygen therapy, continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), or invasively via mechanical ventilation. Children with significant respiratory distress and hypoxaemia often require the latter. This may result in various forms of trauma to the lungs and airways, collectively known as ventilator-induced lung injury (VILI) (Dahlem 2003; The ARDS Network 2000). Although VILI is the major concern with intubation and mechanical ventilation, other effects on the body need to be considered. Increased use of sedative drugs may lead to neuropathy or myopathy, which can increase recovery time. In turn, cardiovascular support in the form of drug infusions may be needed to maintain blood pressure. These requirements increase the costs of care provided to the child. Non-invasive methods of ventilation are an ideal method of providing respiratory support without the need for intubation and may avoid some of the additional harms associated with positive-pressure ventilation, such as ventilator-associated pneumonia (VAP) (Glossop 2012).

Non-invasive ventilation can be as simple as oxygen therapy delivered via face mask, nasal cannula or head box or devices delivering CPAP/BiPAP via face mask or nasopharyngeal tubes, with pressure generated by a dedicated driver or water column (i.e. bubble CPAP) (Frey 2001; Frey 2003; Klein 1986). Devices delivering CPAP/BiPAP can reduce the work of breathing and improve functional residual capacity, potentially avoiding intubation, reducing VILI and VAP and preventing other possible causes of harm (Reid 1984; Thorsteinsson 2002). Disadvantages of this method of delivery are that it is cumbersome, and the masks and tubes are poorly tolerated by young children and infants (McGinley 2009; Spentzas 2009; Yong 2005). Obtaining an adequate seal around the face of small children can be difficult, thereby making delivery of CPAP/BiPAP variable and resulting in ineffective ventilation. This is often due to the limited choice of face masks developed for children with a wide range of ages and stages of facial development. The need for a system that can deliver CPAP while being comfortable and well tolerated by children is an important consideration in providing non-invasive respiratory support.

Description of the intervention

High-flow nasal cannula (HFNC) therapy has recently been introduced for a range of patients from preterm infants to adults, addressing the need for a simple, effective method of providing respiratory support (Campbell 2006; McGinley 2009; McKiernan 2010; Shoemaker 2007). It offers an advantage over simple oxygen therapy in that the gas mixture can be heated and humidified, thereby reducing damage to upper airway mucosa, and the concentration of inspired oxygen can be titrated as required. This can prevent inflammatory reactions and the naso-pulmonary bronchoconstrictor reflex triggered by cold, dry air (Spentzas 2009). The mixed gas is delivered via a nasal cannula that sits just inside the nares. The flow rate delivered varies depending on the type of cannula used but can range from 4 to 70 L/min.

How the intervention might work

It has been shown that delivery of nasal air at high flow rates may cause incidental delivery of CPAP (Dysart 2009; Spence 2007; Wilkinson 2008). The effects of this are yet to be fully understood. It may be that the high flow flushes the dead space of the nasopharyngeal cavity, resulting in alveolar ventilation as a greater fraction of minute ventilation. It may also assist in the washout of carbon dioxide, which may then reduce apnoea secondary to hypercapnia and improve ventilation (Dysart 2009). High flow rates may also provide some amount of positive pressure and thereby overcome upper airway obstruction, again improving ventilation (McGinley 2009).

The amount of CPAP generated depends on the flow delivered relative to the size of the patient, the size of the nasal cannula used and the potential for leak around the nasal cannula (Kubicka 2008; Lampland 2009; Sreenan 2001). Three retrospective studies in paediatric populations assessing HFNC therapy have demonstrated that overall, ventilator days were significantly decreased after introduction of this therapy when compared with retrospective historical control groups (McKiernan 2010; Schibler 2011; Shoemaker 2007). HFNC therapy has also been reported to be better tolerated by the patient than other forms of non-invasive ventilation (Roca 2010). This can reduce the need for the sedation required to help patients tolerate more invasive or uncomfortable forms of respiratory support.

Why it is important to do this review

HFNC therapy is an emerging treatment option for the respiratory support of children, especially in the intensive care unit. To date, most findings have been derived from neonatal and adult studies, with little clinical experience reported in the paediatric population (McKiernan 2010). Clinical experience in the paediatric population is reported in case reports and observational studies; few randomized controlled trials are reported (Mayfield 2013;
McGinley 2009; Spentzas 2009). The Cochrane review of HFNC therapy from the Cochrane Neonatal Group found only four eligible, randomized controlled trials and concluded that evidence was insufficient to determine effectiveness, and more research was needed (Wilkinson 2011). Two further reviews of HFNC therapy are under way: in the adult population (Corley 2012) and in infants with bronchiolitis (Beggs 2012). This review differs in that it includes studies of children with a broader age range and more diverse pathophysiology such as type 1 and 2 respiratory failure, parenchymal lung disease, neuromuscular disorders, respiratory drive disorders and airway obstruction.

HFNC therapy has the potential to improve outcomes such as reduced intubation and invasive ventilation (McKiernan 2010; Schibler 2011; Wing 2012) in critically ill children. It is readily applied and is not resource or cost intensive. Staff can easily be trained in the application of HFNC therapy and in the care of children using this therapy. It may also reduce the length of intubation, as HFNC holds potential to transition between extubation and low-flow nasal cannula oxygen delivery. An additional advantage is that children requiring this therapy may be cared for outside of the paediatric intensive care unit (PICU). However potential risks are associated with its use, such as air leak syndrome, which has been described in a case report (Hedge 2013), and other risks extrapolated from the neonatal population, such as nasal trauma and abdominal overdistention (Kopelman 2003). These potential risks and benefits need to be assessed in the paediatric population.

**OBJECTIVES**

To determine whether HFNC therapy is more effective than other forms of non-invasive therapy in paediatric patients who require respiratory support.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included prospective randomized controlled trials (RCTs) and quasi-randomized studies.

**Types of participants**

We included paediatric participants from four weeks corrected age to 16 years of age requiring respiratory support for type 1 and 2 respiratory failure, parenchymal lung disease, neuromuscular disorders, respiratory drive and airway obstruction. We excluded a study in children with bronchiolitis.

**Types of interventions**

What constitutes ‘high flow’ has not been well described in the literature, nor has it been universally determined. Most paediatric studies have been limited to using devices that deliver flow rates in infants from 4 to 8 L/min (Arora 2012; Schibler 2011). Older children may have up to 30 L/min delivered (McGinley 2009). For the purposes of this review, high-flow nasal oxygen was defined as the delivery of heated, humidified oxygen or blended oxygen with air via nasal cannula at flow rates greater than 2 L/min. HFNC therapy was compared with other means of non-invasive respiratory support, such as cot, hood or tent oxygen; low-flow nasal cannula (flow rates ≤ 2 L/min); and continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP).

**Types of outcome measures**

**Primary outcomes**

1. Hospital mortality.
2. Intubation rate.
3. Treatment failure (defined as the need for additional respiratory support).

**Secondary outcomes**

1. Duration of any form of respiratory support in hours (mechanical ventilation, non-invasive ventilation, high-flow nasal cannula).
2. Length of stay in hospital in days.
3. Clinical severity score.
4. Length of paediatric intensive care unit (PICU) stay in days.
5. Complications.
   - Air leaks (pneumothorax, pneummediastinum, pneumopericardium or pulmonary interstitial emphysema (PIE)) reported individually or as a composite outcome.
   - Nasal trauma (defined as erythema or erosion of the nasal mucosa, nares or septum as assessed by a blinded observer).
   - Barotrauma.
   - Gastrointestinal distention.

**Search methods for identification of studies**

**Electronic searches**

We obtained all relevant studies irrespective of language or publication status (published, unpublished, in press and in progress) using the following methods. We applied no limits in terms of language or year of publication. We searched Issue 4, 2013 of the Cochrane Central Register of Controlled Trials (CENTRAL, see Appendix 1); MEDLINE via
Ovid SP (January 1966 to April 2013, see Appendix 2); EMBASE via Ovid SP (January 1980 to April 2013, see Appendix 3); CINAHL via EBSCO Host (1982 to April 2013, see Appendix 4); and LILACS via the BIREME interface (1982 to April 2013, see Appendix 5).

We also searched the electronic databases of higher-degree theses for relevant unpublished trials: Index to Theses (1950 to date), Australian Digital Theses Program (1997 to April 2013) and Proquest Digital Dissertations (1980 to April 2013).

We then combined our MEDLINE search strategy with the Cochrane highly sensitive search strategy for identifying RCTs, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We adopted the MEDLINE search strategy for searching in all other databases.

For ongoing trials, we searched the MetaRegister of Controlled Trials (http://www.controlledtrials.com/) and the National Research Register (http://clinicaltrials.gov/).

Searching other resources
We handsearched citations from included studies.

Data collection and analysis
We used standard methodological procedures expected by The Cochrane Collaboration.

Selection of studies
We used the search strategy described to obtain titles and abstracts of studies that may be relevant to the review. Two review authors (SM and JJ-C) independently performed this screening. Studies that were not applicable were discarded. We found no ongoing studies that matched our search criteria.

Data extraction and management
We adapted the standardized Cochrane Anesthesia Review Group (CARG) data extraction form (Appendix 6) to capture relevant data specific to this review. We (SM and JJ-C) independently extracted and collected data from the relevant study. No disagreements arose.

Assessment of risk of bias in included studies
No studies were eligible for assessment of risk of bias. However, we planned to assess risk of bias using the following domains with judgements of high, low or uncertain:

1. Selection bias: incorporating random sequence generation and allocation concealment.
2. Performance bias: blinding of participants and personnel.
4. Attrition bias: incomplete outcome data.
5. Reporting bias: selective reporting.
6. Other bias: other sources of bias.

Measures of treatment effect
No studies were found that could be included in this review. Excluded studies were tabulated with the reasons for exclusion documented in the Characteristics of excluded studies.

We planned to manage dichotomous outcome data, such as mortality, by using risk ratios (RRs) to determine effect and by displaying them in a table. For continuous data, we planned to collect means and standard deviations and to display them in a table. If different scales were used to measure continuous data, we would have calculated the standardized mean difference. Outcomes from comparable trials would have used 95% confidence intervals to estimate treatment effect. We would use forest plots to graphically compare treatment effect with risk ratio for dichotomous data and with mean difference for continuous outcomes.

Unit of analysis issues
The unit of analysis was the individual child. We expected to find parallel-group study designs and no cross-over studies. As none of the studies included in this review were randomized at cluster level, unit of analysis was not an issue.

Dealing with missing data
If eligible studies with missing data were found, we planned to contact the corresponding author.

Assessment of heterogeneity
We planned to analyse heterogeneity using the Chi² test on N-1 degrees of freedom, with an alpha of 0.1 used for statistical significance, along with the I² statistic (Higgins 2011).

Assessment of reporting biases
We planned to assess publication bias or small-study effects by preparing a funnel plot. We planned to test for funnel plot asymmetry if more than 10 studies were included in the meta-analysis. We planned to obtain published and unpublished studies as a way of addressing reporting bias.

Data synthesis
We planned to review the summary tables of included trials to identify clinical heterogeneity amongst trials. If two or more randomized trials had been found with comparable populations undergoing similar interventions, we would have conducted a meta-analysis with a random-effects model using RevMan 5.2.
Subgroup analysis and investigation of heterogeneity
No studies were found to permit subgroup analyses or exploration of heterogeneity (Sutton 2008).

Sensitivity analysis
No studies were found to allow sensitivity analysis.

Summary of findings
We planned to use the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with the following specific outcomes in our review.
1. Mortality.
2. Intubation.
3. Failure of treatment or escalation to non-invasive ventilation.
4. Length of PICU stay.
5. Length of time on any form of respiratory support.
6. Oxygenation and respiratory assessment tools. However, no studies were identified for inclusion.

RESULTS

Description of studies
See Characteristics of excluded studies.

Results of the search
Our search yielded 922 records. After duplicates and irrelevant references were removed, 69 were further scrutinized. Eleven studies involved children. No study met our criteria (Figure 1).
Figure 1. Study flow diagram.

900 records identified through database searching

22 additional records identified through other sources such as grey literature, thesis databases and trial register

109 relevant records

58 records excluded
- 8 letters and reviews
- 27 adult
- 18 neonates
- 5 animals/models

69 records after duplicates removed

11 articles excluded
- 1 randomized controlled trial (bronchiolitis)
- 4 retrospective
- 2 observational
- 3 physiological (1 from conference proceedings)
- 1 case series

11 paediatric articles assessed for eligibility
We found no randomized controlled trials of HFNC therapy in children older than four weeks of age requiring respiratory support for type 1 or 2 respiratory failure, parenchymal lung disease, neuromuscular disorders, respiratory drive or airway obstruction.

**Discussion**

**Summary of main results**

We found no randomized controlled trials of HFNC therapy in children older than four weeks of age requiring respiratory support for type 1 or 2 respiratory failure, parenchymal lung disease, neuromuscular disorders, respiratory drive or airway obstruction.

**Overall completeness and applicability of evidence**

N/A.

**Quality of the evidence**

N/A.

**Potential biases in the review process**

We believe that any bias in this review is of low probability. We ensured that language would not be a bias by imposing no restrictions on such. We used a well-constructed search strategy to minimize the chance of missing randomized controlled trials that fulfilled our inclusion criteria.

**Agreements and disagreements with other studies or reviews**

This review supports the conclusion of other studies and reviews conducted to evaluate HFNC therapy (Lee 2013; Wilkinson 2011) in that evidence of robust quality is insufficient to permit determination of the superiority of HFNC therapy over other established forms of non-invasive ventilation for children with moderate to severe respiratory compromise. Further studies are needed to quantify this and to identify clinical indicators regarding its use.

**Authors' conclusions**

**Implications for practice**

Based on the results of this review, no evidence can be found to allow determination of the safety or effectiveness of HFNC therapy as a form of respiratory support in children.

**Implications for research**

It is acknowledged that while the number of retrospective, observational and physiological studies surrounding the support of HFNC therapy for respiratory support in children is increasing, adequately
powered randomized controlled trials are needed. HFNC therapy must be compared with CPAP and other forms of non-invasive respiratory support. Clinically important outcomes, such as escalation to CPAP or intubation, length of stay and duration of treatment, need to be assessed. With such a broad range of ages and disease processes in children, an aim of further research should be to establish which subgroups benefit from HFNC therapy.

**ACKNOWLEDGEMENTS**

We would like to thank Bronagh Blackwood (content editor) and David Turner, Christophe Mileší, Mark W Davies and Oliver Karam (peer reviewers) for their help and editorial advice during the preparation of this systematic review.

We would also like to thank Mathew Zacharis (content editor), Cathal Walsh (statistical editor) and Dominic Wilkinson, Oliver Karam and Mark Davies (peer reviewers) for their help and editorial advice during the preparation of the protocol for the systematic review.

### REFERENCES

**References to studies excluded from this review**

Abboud 2012 [published data only]

Aorora 2012 [published data only]

Hedge 2013 [published data only]

Hilliard 2012 [published data only]

Hough 2011 [published data only]

McGinley 2009 [published data only]

McKernan 2010 [published data only]

Milesi 2013 [published data only]

Schibler 2011 [published data only]

Spentzas 2009 [published data only]

Wing 2012 [published data only]

Additional references

Beggs 2012

Campbell 2006

Corley 2012
Dahlem 2003

Dysart 2009

Frey 2001

Frey 2003

Glossop 2012

Guyatt 2008

Higgins 2011

Klein 1986

Kopelman 2003

Kubicka 2008
Kubicka ZJ, Limauro J, Darnell RA. Heated humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure?. *Pediatrics* 2008;121:82–8. [PUBMED: 18166560]

Lampland 2009

Lee 2013

Mayfield 2013

Reid 1984

RevMan 5.2

Roca 2010

Shoemaker 2007

Spence 2007

Sreenan 2001

Sutton 2008

The ARDS Network 2000

Thorsteinsson 2002
Thorsteinsson A, Werner O, Jonnaker C, Larsson A. Airway closure in anaesthetized infants and children: the influence

**Wilkinson 2008**


**Wilkinson 2011**


**Yong 2005**


**References to other published versions of this review**

**Mayfield 2012**


* Indicates the major publication for the study
## Characteristics of excluded studies  
**[ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Abboud 2012</td>
<td>Retrospective chart review of all patients admitted to intensive care with a diagnosis of viral bronchiolitis from 2006 to 2010. 113 patients met inclusion criteria of &lt; 12 months, initiation of HFNC on admission</td>
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<tr>
<td>Arora 2012</td>
<td>Prospective observational study to measure nasopharyngeal effects of HFNC in infants with bronchiolitis. 25 infants enrolled</td>
</tr>
<tr>
<td>Hedge 2013</td>
<td>Case series of three patients with air leak syndrome who were also treated with HFNC</td>
</tr>
<tr>
<td>Hilliard 2012</td>
<td>Prospective randomized controlled trial comparing HFNC versus head box oxygen therapy. 19 participants enrolled, all with viral bronchiolitis</td>
</tr>
<tr>
<td>Hough 2011</td>
<td>Prospective physiological study comparing HFNC at different flow rates. 13 participants enrolled, all with bronchiolitis</td>
</tr>
<tr>
<td>McGinley 2009</td>
<td>Prospective observational study of 12 participants with obstructive apnoea-hypopnoea syndrome treated with nasal insufflation at 20 L/min</td>
</tr>
<tr>
<td>McKiernan 2010</td>
<td>Retrospective chart review comparing intubation rates of infants with bronchiolitis admitted before and in the season after HFNC was implemented. 115 participants included in the review</td>
</tr>
<tr>
<td>Milesi 2013</td>
<td>Prospective physiological study of 21 infants &lt; six months with viral bronchiolitis and HFNC therapy. Pharyngeal and oesophageal pressures measured at different flow rates</td>
</tr>
<tr>
<td>Schibler 2011</td>
<td>Retrospective chart review of infants &lt; 24 months admitted to PICU between January 2005 and December 2009, requiring HFNC therapy. 298 infants included in the review</td>
</tr>
<tr>
<td>Spentzas 2009</td>
<td>Observational study of all participants (newborn to 12 years) requiring HFNC, admitted between January 2005 and January 2007 to PICU. 46 participants included in the study</td>
</tr>
<tr>
<td>Wing 2012</td>
<td>Retrospective chart review of all patients admitted from ED to PICU with acute respiratory insufficiency from January 2006 to December 2009. Patients admitted before HFNC availability were compared with patients admitted after HFNC became available (two cohorts, before and after implementation of clinical guidelines). 848 participants included in the review</td>
</tr>
</tbody>
</table>
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy
#1 MeSH descriptor Oxygen Inhalation Therapy explode all trees
#2 intubation rates*
#3 (#1 AND #2)
#4 ((high flow (nasal or prong or cannula)) or (nasal near oxygen)):ti,ab
#5 (#3 OR #4)
Search from Issue 4 2013.

Appendix 2. MEDLINE (Ovid SP) search strategy
1. (exp Oxygen Inhalation Therapy/ and intubation rates*.af.) or (high flow adj3 (nasal or prong or cannula)).mp. or (nasal adj3 oxygen).mp.
2. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
3. 1 and 2
Search from January 1966- April 2013.

Appendix 3. EMBASE (Ovid SP) search strategy
1. (exp oxygen therapy/ and intubation rates*.af.) or (high flow adj3 (nasal or prong or cannula)).mp. or (nasal adj3 oxygen).mp.
2. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross*over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.
3. 1 and 2
Search from January 1980 to April 2013.

Appendix 4. CINAHL (EBSCO host) search strategy
S1 (((MH “Oxygen Therapy”) and intubation rates*)) OR ((high flow and (nasal or prong or cannula))) OR (nasal and oxygen)
S2 (MM “Randomized Controlled Trials”) OR (MM “Random Assignment”) OR (MH “Clinical Trials”) OR (MM “Multicenter Studies”) OR (MM “Prospective Studies”) OR (MM “Placebos”) OR (MM “Double-Blind Studies”) OR (MM “Triple-Blind Studies”) OR (MM “Single-Blind Studies”)
S3 S1 and S2
Search from 1982-April 2013.
Appendix 5. LILACS search strategy

(oxygen therapy and intubation rates$) or (high flow and (nasal or prong or cannula)) or (nasal and oxygen) [Palabras]
Search from 1982 to April 2013.

Appendix 6. Data extraction form

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<tr>
<th>Study ID (surname of first author and year first full report of study was published e.g. Smith 2001)</th>
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<th>Report IDs of other reports of this study (e.g. duplicate publications, follow-up studies)</th>
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I. General information

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</tbody>
</table>

<table>
<thead>
<tr>
<th>Name/ID of person extracting data</th>
</tr>
</thead>
<tbody>
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</table>

<table>
<thead>
<tr>
<th>Report title (title of paper/abstract/report from which data are extracted)</th>
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<tbody>
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</tbody>
</table>
2. Study eligibility

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Eligibility criteria (insert eligibility criteria for each characteristic as defined in the protocol)</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Location in text (pg &amp; fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Randomized controlled trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controlled clinical trial (quasi-randomized trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Paediatric patients from four weeks corrected to 16 years of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of interventions</td>
<td>High-flow nasal oxygen (heated/humidified, flow &gt; 2 L/kg/min) Comparator: non-invasive respiratory support such as cot/tent/hood, low-flow oxygen or CPAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Types of outcome measures

| Hospital mortality; intubation rate; treatment failure |
| Secondary: duration of any form of respiratory support; length of hospital stay; clinical severity score; length of PICU stay; complications-air leak, nasal trauma, nosocomial sepsis, barotrauma, gastrointestinal distention |

INCLUDE

EXCLUDE

Reason for exclusion

Notes:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW.

3. Methods

Aim of study

Design (e.g. parallel, cross-over, cluster)

Unit of allocation (by individuals, cluster/groups or body parts)

Start date

End date

Total study duration
Ethical approval needed/obtained for study

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
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</thead>
<tbody>
<tr>
<td>Notes</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

4. Risk of bias assessment

See Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

<table>
<thead>
<tr>
<th>Domain</th>
<th>Risk of bias</th>
<th>Support for judgement</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td></td>
<td></td>
<td>Outcome group: all/</td>
</tr>
<tr>
<td>(if required)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td></td>
<td></td>
<td>Outcome group: all/</td>
</tr>
<tr>
<td>(if required)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective outcome reporting? (reporting bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. randomly assigned</td>
<td></td>
</tr>
<tr>
<td>(or total population at start of study for NRCTs)</td>
<td></td>
</tr>
<tr>
<td>Clusters</td>
<td></td>
</tr>
<tr>
<td>(if applicable, no., type, no. people per cluster)</td>
<td></td>
</tr>
<tr>
<td>Withdrawals and exclusions</td>
<td></td>
</tr>
<tr>
<td>(if not provided below by outcome)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Severity of illness</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Other treatment received</td>
<td></td>
</tr>
<tr>
<td>(additional to study intervention)</td>
<td></td>
</tr>
<tr>
<td>Subgroups measured</td>
<td></td>
</tr>
<tr>
<td>Subgroups reported</td>
<td></td>
</tr>
<tr>
<td>Notes:</td>
<td></td>
</tr>
</tbody>
</table>
### Intervention group 1

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group name</td>
<td>HFNC</td>
</tr>
<tr>
<td>No. randomly assigned to group</td>
<td></td>
</tr>
<tr>
<td>(specify whether no. people or clusters)</td>
<td></td>
</tr>
<tr>
<td>Description (include sufficient detail for replication, e.g. content, dose, components)</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment period</td>
<td></td>
</tr>
<tr>
<td>Timing (e.g. frequency, duration of each episode)</td>
<td></td>
</tr>
<tr>
<td>Delivery (e.g. mechanism, medium, intensity, fidelity)</td>
<td></td>
</tr>
<tr>
<td>Co-interventions</td>
<td></td>
</tr>
<tr>
<td>Notes:</td>
<td></td>
</tr>
</tbody>
</table>

### Comparison group 1

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group name</td>
<td>Invasive ventilation</td>
</tr>
<tr>
<td>No. randomly assigned to group</td>
<td></td>
</tr>
<tr>
<td>(specify whether no. people or clusters)</td>
<td></td>
</tr>
<tr>
<td>Description (include sufficient detail for replication, e.g. content, dose, components)</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment period</td>
<td></td>
</tr>
<tr>
<td>Timing (e.g. frequency, duration of each episode)</td>
<td></td>
</tr>
</tbody>
</table>
Comparison group 2

<table>
<thead>
<tr>
<th>Group name</th>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive ventilation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **No. randomly assigned to group** (specify whether no. people or clusters)
- **Description** (include sufficient detail for replication, e.g. content, dose, components)
- **Duration of treatment period**
- **Timing** (e.g. frequency, duration of each episode)
- **Delivery** (e.g. mechanism, medium, intensity, fidelity)
- **Co-interventions**
- **Notes**

7. **Outcomes**

*Copy and paste table for each outcome.*

**Outcome 1**
<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time points measured</td>
<td></td>
</tr>
<tr>
<td>Time points reported</td>
<td></td>
</tr>
<tr>
<td>Outcome definition</td>
<td>(with diagnostic criteria if relevant)</td>
</tr>
<tr>
<td>Person measuring/reporting</td>
<td></td>
</tr>
<tr>
<td>Unit of measurement</td>
<td>(if relevant)</td>
</tr>
<tr>
<td>Scales: upper and lower limits</td>
<td>(indicate whether high or low score is good)</td>
</tr>
<tr>
<td>Is outcome/tool validated?</td>
<td>Yes No Unclear</td>
</tr>
<tr>
<td>Imputation of missing data</td>
<td>(e.g. assumptions made for ITT analysis)</td>
</tr>
<tr>
<td>Assumed risk estimate</td>
<td>(e.g. baseline or population risk noted in Background)</td>
</tr>
<tr>
<td>Power</td>
<td></td>
</tr>
<tr>
<td>Notes:</td>
<td></td>
</tr>
</tbody>
</table>

**Outcome 2**

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Intubation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description as stated in report/paper</td>
<td></td>
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<tr>
<td>Location in text (pg &amp; /fig/table)</td>
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</tr>
<tr>
<td>Time points measured</td>
<td></td>
</tr>
<tr>
<td>Time points reported</td>
<td></td>
</tr>
<tr>
<td>Outcome definition <em>(with diagnostic criteria if relevant)</em></td>
<td></td>
</tr>
<tr>
<td>Person measuring/reporting</td>
<td></td>
</tr>
<tr>
<td>Unit of measurement <em>(if relevant)</em></td>
<td></td>
</tr>
<tr>
<td>Scales: upper and lower limits <em>(indicate whether high or low score is good)</em></td>
<td></td>
</tr>
<tr>
<td>Is outcome/tool validated?</td>
<td>Yes</td>
</tr>
<tr>
<td>Imputation of missing data <em>(e.g. assumptions made for ITT analysis)</em></td>
<td></td>
</tr>
<tr>
<td>Assumed risk estimate <em>(e.g. baseline or population risk noted in Background)</em></td>
<td></td>
</tr>
<tr>
<td>Power</td>
<td></td>
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<tr>
<td>Notes:</td>
<td></td>
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</tbody>
</table>

### Outcome 3

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text <em>(pg &amp; ¶/fig/table)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure-escalation to other form of respiratory support</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Time points measured</th>
<th>Time points reported</th>
<th>Outcome definition <em>(with diagnostic criteria if relevant)</em></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Person measuring/reporting</td>
<td>Unit of measurement (if relevant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------------</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scales: upper and lower limits (indicate whether high or low score is good)</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is outcome/tool validated?</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
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</table>

<table>
<thead>
<tr>
<th>Imputation of missing data (e.g. assumptions made for ITT analysis)</th>
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<table>
<thead>
<tr>
<th>Assumed risk estimate (e.g. baseline or population risk noted in Background)</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Power</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Notes:</th>
<th></th>
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</table>

**Outcome 4**

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
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<tbody>
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<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Duration of respiratory support</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time points measured</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Time points reported</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome definition (with diagnostic criteria if relevant)</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Person measuring/reporting</th>
<th>Unit of measurement (if relevant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Outcome 5

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
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</thead>
<tbody>
<tr>
<td>Complications-air leak, nasal trauma, nosocomial sepsis, baro-trauma, gastrointestinal distention</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Complications-air leak, nasal trauma, nosocomial sepsis, baro-trauma, gastrointestinal distention</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Time points measured</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Time points reported</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome definition (with diagnostic criteria if relevant)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Person measuring/reporting</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit of measurement (if relevant)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Scales: upper and lower limits (indicate whether high or low score is good)</th>
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(Continued)
<table>
<thead>
<tr>
<th>Outcome 6</th>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Length of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Time points measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time points reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome definition</td>
<td>(with diagnostic criteria if relevant)</td>
<td></td>
</tr>
<tr>
<td>Person measuring/reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unit of measurement</td>
<td>(if relevant)</td>
<td></td>
</tr>
<tr>
<td>Scales: upper and lower limits</td>
<td>(indicate whether high or low score is good)</td>
<td></td>
</tr>
<tr>
<td>Is outcome/tool validated?</td>
<td>Yes No Unclear</td>
<td></td>
</tr>
<tr>
<td>Imputation of missing data</td>
<td>(e.g. assumptions made for ITT analysis)</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Assumed risk estimate</td>
<td>(e.g. baseline or population risk noted in Background)</td>
<td></td>
</tr>
<tr>
<td>Power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Outcome 7

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome name</strong></td>
<td>Clinical severity score</td>
</tr>
<tr>
<td><strong>Time points measured</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Time points reported</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome definition</strong></td>
<td>(with diagnostic criteria if relevant)</td>
</tr>
<tr>
<td><strong>Person measuring/reporting</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Unit of measurement</strong></td>
<td>(if relevant)</td>
</tr>
<tr>
<td><strong>Scales: upper and lower limits</strong></td>
<td>(indicate whether high or low score is good)</td>
</tr>
<tr>
<td><strong>Is outcome/tool validated?</strong></td>
<td>Yes No Unclear</td>
</tr>
<tr>
<td><strong>Imputation of missing data</strong></td>
<td>(e.g. assumptions made for ITT analysis)</td>
</tr>
</tbody>
</table>
Outcome 8: secondary outcome

<table>
<thead>
<tr>
<th>Assumed risk estimate (e.g. baseline or population risk noted in Background)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
</tr>
<tr>
<td>Notes:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of PICU stay</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time points measured</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Time points reported</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome definition (with diagnostic criteria if relevant)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Person measuring/reporting</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit of measurement (if relevant)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Scales: upper and lower limits (indicate whether high or low score is good)</th>
</tr>
</thead>
</table>

| Is outcome/tool validated? | Yes No Unclear |
|---|---|---|

<table>
<thead>
<tr>
<th>Imputation of missing data (e.g. assumptions made for ITT analysis)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Assumed risk estimate (e.g. baseline or population risk noted in Background)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Power</th>
</tr>
</thead>
</table>
### 8. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

#### Dichotomous outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HFNC</th>
<th>Invasive ventilation</th>
<th>Non-invasive ventilation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with event</td>
<td>No. without event</td>
<td>No. with event</td>
<td>No. without event</td>
</tr>
<tr>
<td>Intubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### Continuous outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unit of measurement</th>
<th>HFNC group</th>
<th>Invasive ventilation group</th>
<th>Non-invasive group</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M</td>
<td>SD</td>
<td>n</td>
<td>M</td>
</tr>
<tr>
<td>Length of PICU stay</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Clinical severity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(Continued)

<table>
<thead>
<tr>
<th>Duration of respiratory support</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS Hospital</td>
<td></td>
</tr>
</tbody>
</table>

### 9. Applicability

<table>
<thead>
<tr>
<th>Have important populations been excluded from the study? (consider disadvantaged populations and possible differences in the intervention effect)</th>
<th>Yes No Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the intervention likely to be aimed at disadvantaged groups? (e.g., lower socio-economic groups)</td>
<td>Yes No Unclear</td>
</tr>
<tr>
<td>Does the study directly address the review question? (any issues of partial or indirect applicability)</td>
<td>Yes No Unclear</td>
</tr>
</tbody>
</table>

#### Notes:

### 10. Other information

<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusions of study authors</td>
<td></td>
</tr>
<tr>
<td>References to other relevant studies</td>
<td></td>
</tr>
</tbody>
</table>
Correspondence required for further study information (from whom, what and when)

Notes:

**CONTRIBUTIONS OF AUTHORS**

Conceiving of the review: Sara Mayfield (SM).
Co-ordinating the review: SM.
Undertaking manual searches: SM.
Screening search results: SM and Jacqui Jauney-Cooke (JJ-C).
Organizing retrieval of papers: SM.
Screening retrieved papers against inclusion criteria: SM and JJ-C.
Abstracting data from papers: SM and JJ-C.
Writing to authors of papers for additional information: SM.
Providing additional data about papers: SM.
Obtaining and screening data on unpublished studies: SM.
Managing data for the review: SM, JJ-C and Fiona Bogossian (FB).
Entering data into Review Manager (**RevMan 5.2**): SM.
Writing the review: SM.
Serving as guarantor for the review (one author): FB.
Taking responsibility for reading and checking the review before submission: JJ-C, FB, AS and JH.
DECLARATIONS OF INTEREST

Sara Mayfield and Andreas Schibler have received financial and equipment support from Fisher Paykel Healthcare to conduct two observational studies involving HFNC therapy. These studies would not be eligible for inclusion in this review.

Jacqueline Jauncey-Cooke: none known.
Judith L Hough: none known:
Kristen Gibbons: none known.
Fiona Bogossian: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Initially we planned to include all paediatric patients requiring HFNC therapy; however, because of the overlap with another Cochrane Review of HFNC in infants with bronchiolitis (Beggs 2012), we excluded children with bronchiolitis from our review.
4.3 Conclusion

At the time of preparing this thesis (mid-2014), the protocol (Appendix 1) and review have been completed and published with CARG as evidenced above. The protocol with the Neonatal Review Group is published and the review is expected to be completed late 2014/early 2015. Following that, both reviews are scheduled for revision in two years.

The following chapter will detail the methodology for a pilot study, undertaken in the paediatric ward setting, using HFNC in the management of infants with bronchiolitis.
Chapter 5: Pilot study methodology

5.1 Introduction

The previous chapters of this thesis outlined bronchiolitis – its history, sequelae, health service response, and the various pharmacological and non-pharmacological treatment options; and HFNC oxygen therapy – mechanism of action, current evidence available, and a case series of its use in the intensive care setting. The previous chapters also presented a Cochrane Review examining the evidence for HFNC.

To advance understanding and raise the level of evidence for using HFNC therapy beyond the ICU, experimental studies are required. This chapter reports the methodology of the pilot study, which aimed to assess the safety and efficacy of HFNC therapy outside intensive care. The pilot study used a paediatric ward setting and, in the absence of a specific reporting framework for pilot studies, it used the TREND guidelines and checklist167 to guide reporting where appropriate.

5.1.1 Background

Bronchiolitis is the leading cause of paediatric hospitalisation in Australia accounting for approximately 16,000 admissions annually.42 Treatment of bronchiolitis is controversial, and many RCTs have been conducted without showing a clear benefit for any specific treatment. Most of these trials attempted to reduce either the inflammatory response (using steroids) or smooth muscle relaxation of the small airways (using adrenaline, salbutamol). No studies, however, provide data investigating whether reducing the work of breathing through moderate respiratory support improves length of stay, reduces admission rates to PICU, or the need for intubation.

5.2 Research questions

HFNC is a rapidly emerging clinical therapy used in the intensive care setting to treat respiratory distress in populations from neonates to adults. Based on the observed high efficacy and practicality of using HFNC in PICUs, there is a desire to implement its use in general paediatric wards. However, several unanswered questions remain before HFNC can become standard practice for delivering oxygen to patients with respiratory distress in the general paediatric ward:
• Is safety of HFNC treatment in a general paediatric ward similar to in PICU?
• Does HFNC treatment reduce the hospital length of stay (LOS)?
• Does the early use of HFNC reduce the number of PICU admissions?
• Does the early use of HFNC reduce the need to use non-invasive and invasive ventilation?

5.3 Study aim

This pilot study aimed to assess the safety and efficacy of managing infants with bronchiolitis on a paediatric ward with HFNC therapy. The measures used as surrogates to determine safety and efficacy were admission to PICU, physiological response to HFNC, adverse events (bradycardia, pneumothorax, cardiopulmonary arrest and emergency intubation), and hospital and PICU length of stay. A secondary aim was to determine a sample size for a future, large multi-centred RCT.

5.4 Outcome measures

The primary outcome measure was admission to PICU. This was readily tracked prospectively as every study participant was visited on a daily basis, Monday to Friday.

Secondary outcome measures encompassed physiological response to HFNC therapy and were collected on the HiFOD form. These measures included respiratory, cardiovascular and overall HiFOD score. Adverse events (including bradycardia, pneumothorax, cardiopulmonary arrest and emergency intubation) were also defined as outcome measures and were collected prospectively for all patients. Other outcome measures collected were the need for non-invasive ventilation and/or intubation for those patients admitted to PICU, as well as hospital and PICU length of stay.

5.5 Study design

Pilot designed studies are a useful way to determine processes, resources, management and assessment of treatment safety that influence and govern large, multi-centred RCTs. For this study, a pilot design was chosen to explore the safety and efficacy of implementing HFNC therapy in the paediatric ward environment.

The pilot study encompassed three stages: the education and training of staff involved in the pilot; the recruitment and clinical course of study patients; and data collection and analysis.
5.6 Study setting

The study was located in the PED and the Babies Ward (8 South) of the Mater Children's Hospital (MCH), Brisbane, Australia. In 2009, the Babies Ward had approximately 5580 occupied bed-days. This comprised infants aged less than 12 months, with a case mix including all paediatric medical and surgical specialities, excluding cardiac. The standard nurse to patient ratio is 1:3. For the purpose of the study, nurse to patient ratios remained at 1:3 for study patients. Nursing staff mix per shift comprises at least two clinical nurses (with one designated as team leader), senior registered nurses, junior registered nurses and 1–2 graduate nurses. On week days, a Nurse Unit Manager and Clinical Nurse Educator (CNE) are also present, who provide further managerial and educational support to the nursing team.

5.7 Participants

Potential patients were screened in the PED for inclusion in the study, either at triage or in the acute observation area. The author conducted the initial recruitment of patients from 9am–5pm, Monday to Friday, with PED staff trained to recruit patients outside of these hours.

5.7.1 Inclusion criteria

Infants were considered for study inclusion if they met the following criteria:

- age less than 12 months
- clinical diagnosis of bronchiolitis
- an oxygen requirement, based on oxygen saturations <94% in room air.

Inclusion criteria were selected on the basis that bronchiolitis is the leading cause of hospitalisation in infants less than 2 years of age. To maximise homogeneity of included participants and to focus the study in one ward of the hospital only infants aged less than 12 months of age were to be included.

5.7.2 Exclusion criteria

Infants were excluded from the study if they met any of the following criteria:

- craniofacial malformations
- upper airway obstruction
- home oxygen therapy for pre-existing lung disease
impending PICU admission due to decreasing level of consciousness, apnoeas, need for increased respiratory support (non-invasive or invasive ventilation)

- no oxygen requirement.

5.8 Intervention

5.8.1 Education and training

The education program followed the Mater Education Centre (MEC) Governance & Management Framework. This framework aims to maintain a 'commitment to safe and compassionate care', applying high standards in education, delivered in a strategic, coordinated and collaborative manner to develop capable and safe staff. To ensure the remit of the MEC was adhered to and maintained, funding was applied to employ a part-time CNE to assist in educating staff involved with the study, and to liaise with the MEC, ensuring the proper processes were followed.

The education program consisted of group and individual teaching sessions and commenced a month before the study commenced recruitment. It concentrated on medical and nursing staff in PED, and the ward. It was anticipated that the program would also be a continuous process throughout the recruitment period.

The features of the education program included:

- A focus on two departments in the MCH: PED and the Babies Ward.
- Use of the approved education MEC Governance & Management Framework.
- A structured approach in delivering education, using presentations and utilising set and opportunistic times for education, to ensure staff in the two departments had the knowledge and skills to adhere to the study protocol, and provide the standard care (in accordance with hospital policy) for the infant admitted with bronchiolitis.
- External support from the MCH Acting Nursing Director and the Nurse Unit Managers, and internal support from registered nurses and clinical nurses, ensuring practice change was successfully adopted.

The supported education was essential to the successful completion of the study. It encompasses not only the use of the equipment and the protocol, but using the study's key documentation format: the high flow oxygen data collection form (HiFOD) (Figure 5.1).
5.8.2 Data collection

5.8.2.1 HiFOD data collection form
When considering how to capture physiological data in the initial planning phases of the protocol, it was suggested that the Respiratory Distress Assessment Instrument (RDAI) (Table 5.1) be used to rate respiratory distress as a measure of severity of bronchiolitis.

This instrument has been widely used in papers quantifying the severity of bronchiolitis.\textsuperscript{54,170–172} The RDAI validity was established by comparing chest wall retractions with other work-of-breathing markers, such as breath sounds, grunting, and nasal flaring.\textsuperscript{173} However, this tool had not been used at MCH in any clinical inpatient area, and other available tools were more comprehensive and could have better suited this study.
**Figure 5.1 – High flow oxygen data collection form (HiFOD)**

**HiFOD Scoring Form**

<table>
<thead>
<tr>
<th><strong>URN:</strong></th>
<th>&gt;55</th>
<th>&gt;55</th>
<th>&gt;55</th>
<th>&gt;55</th>
<th>&gt;55</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family Name:</strong></td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td><strong>Given name(s):</strong></td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Date of birth:</strong></td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td>□ M</td>
<td>□ F</td>
<td>□ I</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**HiFOD Score**

- **Severe**
- **Moderate**
- **Mild**

If an observation moves into one of the shaded areas, add up the patient's full HiFOD score and take action as described in the actions box below.

**HiFOD Action**

- Carry out and document appropriate interventions as prescribed.
- Increase frequency of observations.
- Manage pain/fever/anxiety.
- Notify Team Leader as appropriate.
- Register to review patient response within 15 minutes.
- Register for a full score after any interventions.
- Notify Team Leader.
- Ensure consultant is notified.

**Actions**

1 to 2
- Manage pain/fever/anxiety.
- Increase frequency of observations.
- Notify Team Leader as appropriate.
- Register to review patient response within 15 minutes.
- Register for a full score after any interventions.
- Notify Team Leader.
- Ensure consultant is notified.

3 to 6
- Register for a full score after any interventions.
- Notify Team Leader.
- Ensure consultant is notified.

>6
- Place SERT call.
- Register to review patient response within 15 minutes.
- Notify Team Leader.
- Ensure consultant is notified.

**HFOD Score**

<table>
<thead>
<tr>
<th><strong>Score 0</strong></th>
<th><strong>Score 1</strong></th>
<th><strong>Score 2</strong></th>
<th><strong>Score 3</strong></th>
<th><strong>Score 4</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>&gt;30-60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>&gt;30-60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>&gt;30-60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>&gt;30-60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
<td>&gt;60%</td>
</tr>
</tbody>
</table>

**Place emergency call if any of the following:**
- Bradyarrythmia
- Respiratory failure
- Intracerebral hemorrhage
- Respiratory distress
- Unconscious
- Uncontrolled hypertension
- Airway threat
- Apnoea
- Seizure

**Total HiFOD Score**
Since a ‘new’ tool was required to capture the physiological data, paediatric early warning tools were considered. These early warning tools were originally developed and embraced as a consequence of poor identification of – and response to – deteriorating patients, in both adult and paediatric populations. The vast majority of adverse events do not occur through malice or incompetence; in fact, deficiencies in the structure of healthcare systems in the developed world have been identified as the culprit. Some of these systems issues identified in the literature\textsuperscript{174–176} include:

- inability of medical and nursing staff at all levels to recognise critical illness and the deteriorating patient\textsuperscript{174}
- inexperience of doctors reviewing the patient\textsuperscript{175}
- lack of empowerment of junior staff to speak up, or seek senior assistance\textsuperscript{174}
- communication issues between staff\textsuperscript{176}
- errors in diagnosis, delays in instituting therapy, and an inadequate level of intervention.\textsuperscript{175}

As a consequence, the relationship between physiological abnormalities and the occurrence of serious adverse events was considered. Systems that ‘track and trigger’ have been increasingly researched,\textsuperscript{177} based on the periodic measurement of vital signs (track), with a pre-determined response (trigger) at a certain threshold.\textsuperscript{14}

Before the pilot study, MCH had no paediatric warning system in place for the early detection of the deteriorating child. However, as of 2010, five early warning systems

---

**Table 5.1 – Respiratory Distress Assessment Instrument**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Wheezing</td>
<td></td>
</tr>
<tr>
<td>During expiration</td>
<td>None</td>
</tr>
<tr>
<td>During inspiration</td>
<td>None</td>
</tr>
<tr>
<td>No. of involved lung fields</td>
<td>0</td>
</tr>
<tr>
<td>Retractions</td>
<td></td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>None</td>
</tr>
<tr>
<td>Intercostal</td>
<td>None</td>
</tr>
<tr>
<td>Subcostal</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>
existed designed for children, four of which use scoring tools to aid in detecting the deteriorating child.\textsuperscript{178–181} While one of these systems does not use a specific scoring tool, it does provide guidelines for activating medical emergency teams (METs). These METs can be activated by any member of staff, either from a change in clinical state of the patient or simply because the staff are concerned. The system is not dependent on traditional hierarchical medical structures to instigate a review.\textsuperscript{178}

One study identifies that, of the systems using a scoring tool, 78% of "code blue" emergency call patients were recognisable at least one hour before the emergency call.\textsuperscript{179} Other studies have also commented on the improved confidence of the attending staff, and overall staff perceived that they were better able to care for their patients.\textsuperscript{180,181}

Three of the four tools considered have been published.\textsuperscript{179–181} They vary considerably in the way physiological variables are collected and scored (Tables 5.2–5.4). And while they all assess the respiratory and cardiovascular system, they also vary in assessing neurological function, oxygen requirement and airway obstruction. Only one has differentiated between paediatric age groups.\textsuperscript{179} What is similar is that each component generates a score, and the overall score determines the clinician's level of intervention, whether it be obtaining a medical review in a pre-determined time, or instigating an emergency call.

| Table 5.2 – Brighton Paediatric Early Warning Score\textsuperscript{181} |
|---|---|---|---|---|
| Behaviour | 1 | 2 | 3 | Score |
| Behaviour | Playing/appropriate | Sleeping | Irritable | Lethargic/confused. Reduced response to pain. |
| Cardiovascular | Pink or capillary refill 1–2 seconds | Pale or capillary refill 3 seconds | Grey or capillary refill 4 seconds | Grey and mottled or capillary refill 5 seconds or above. Tachycardia of 30 above normal rate or bradycardia. |
| Respiratory | Within normal parameters, no tracheal tug | >10 above normal parameters, using 30+% FiO\textsubscript{2} or 4+ L/min | Tachycardia of 20 above normal rate parameters recessing, tracheal tug. 40+% FiO\textsubscript{2} or 6+ L/min | 5 below normal parameters with sternal recession, tracheal tug or grunting. 50% FiO\textsubscript{2} or 8+ L/min |

Score 2 extra for 1/4 hourly nebulisers or persistent vomiting following surgery
<table>
<thead>
<tr>
<th></th>
<th>Age group</th>
<th>Item sub score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>0 to &lt;3 months</td>
<td>&gt;110 and &lt;150</td>
<td>≥150 or ≤110</td>
<td>≥180 or ≤90</td>
<td>≥190 or ≤80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 to &lt;12 months</td>
<td>&gt;100 and &lt;150</td>
<td>≥150 or ≤100</td>
<td>≥170 or ≤80</td>
<td>≥180 or ≤70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–4 years</td>
<td>&gt;90 and &lt;120</td>
<td>≥120 or ≤90</td>
<td>≥150 or ≤70</td>
<td>≥170 or ≤60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4–12 years</td>
<td>&gt;70 and &lt;110</td>
<td>≥110 or ≤70</td>
<td>≥130 or ≤60</td>
<td>≥150 or ≤50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12 years</td>
<td>&gt;60 and &lt;100</td>
<td>≥100 or ≤60</td>
<td>≥120 or ≤50</td>
<td>≥140 or ≤40</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>0 to &lt;3 months</td>
<td>&gt;60 and &lt;80</td>
<td>≥80 or ≤60</td>
<td>≥100 or ≤50</td>
<td>≥130 or ≤45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 to &lt;12 months</td>
<td>&gt;80 and &lt;100</td>
<td>≥100 or ≤80</td>
<td>≥120 or ≤70</td>
<td>≥150 or ≤60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–4 years</td>
<td>&gt;90 and &lt;110</td>
<td>≥110 or ≤90</td>
<td>≥125 or ≤75</td>
<td>≥160 or ≤65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4–12 years</td>
<td>&gt;90 and &lt;120</td>
<td>≥120 or ≤90</td>
<td>≥140 or ≤80</td>
<td>≥170 or ≤70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12 years</td>
<td>&gt;80 and &lt;100</td>
<td>&gt;100 and &lt;130</td>
<td>≥130 or ≤100</td>
<td>≥150 or ≤85</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥190 or ≤75</td>
<td></td>
</tr>
<tr>
<td><strong>Capillary refill time</strong></td>
<td>&lt;3 seconds</td>
<td></td>
<td></td>
<td></td>
<td>≥3 seconds</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory rate (breaths/ min)</strong></td>
<td>0 to &lt;3 months</td>
<td>&gt;29 and &lt;61</td>
<td>≥61 or ≤29</td>
<td>≥81 or ≤19</td>
<td>≥91 or ≤15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 to &lt;12 months</td>
<td>&gt;24 or &lt;51</td>
<td>≥51 or ≤24</td>
<td>≥71 or ≤19</td>
<td>≥81 or ≤15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–4 years</td>
<td>&gt;19 or &lt;41</td>
<td>≥41 or ≤19</td>
<td>≥61 or ≤15</td>
<td>≥71 or ≤12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4–12 years</td>
<td>&gt;19 or &lt;31</td>
<td>≥31 or ≤19</td>
<td>≥41 or ≤14</td>
<td>≥51 or ≤10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12 years</td>
<td>&gt;11 or &lt;17</td>
<td>≥17 or ≤11</td>
<td>≥23 or ≤10</td>
<td>≥30 or ≤9</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory effort</strong></td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe increase / any apnoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oxygen saturation (%)</strong></td>
<td>&gt;94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91 to 94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oxygen therapy</strong></td>
<td>Room air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any to &lt;4 L/min or &lt;50%</td>
<td></td>
<td></td>
<td>≥4 L/min or ≥50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5.4 – Bristol Paediatric Early Warning Tool

<table>
<thead>
<tr>
<th></th>
<th>Acute airway obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(1) Child has required nebulised adrenaline</td>
</tr>
<tr>
<td></td>
<td>(2) Clinically tiring or impending complete airway obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>(1) SaO₂ ≥92% in any amount of oxygen</td>
</tr>
<tr>
<td></td>
<td>(2) SaO₂ ≥75% in any amount of oxygen (cyanotic heart disease)</td>
</tr>
<tr>
<td></td>
<td>(3) Persistent tachypnoea (RR≥70 under 6 months; ≥60 6–12 months; ≥40 1–5 years; ≥25 over 5 years)</td>
</tr>
<tr>
<td></td>
<td>(4) Apnoea±bradycardia (HR≥95 in children under 5 years)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>(1) Persistent tachycardia following one bolus of 10 ml/kg fluid (HR≥150 under 5 years; HR≥120 5–12 years; HR≥100 over 12 years)</td>
</tr>
<tr>
<td></td>
<td>(2) Signs of shock, e.g. prolonged capillary refill (3 s); poor perfusion; ±low BP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>(1) GCS≥11 or unresponsive or responding only to pain</td>
</tr>
<tr>
<td></td>
<td>(2) Convulsion unresponsive to anticonvulsant therapy (lasting ≥30 min)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>(1) Hyperkalaemia – K+ ≥6.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>(2) Any child with suspected meningococcal disease</td>
</tr>
<tr>
<td></td>
<td>(3) Any child with diabetic ketoacidosis (DKA)</td>
</tr>
<tr>
<td></td>
<td>(4) Any child whose condition is worrying</td>
</tr>
</tbody>
</table>

The fourth tool considered has not been published, however is in use throughout Queensland Health hospitals. The Children’s Early Warning Tool (CEWT, Appendix 3) is very similar to the Bedside PEWSS, and has been developed for differing ages groups in paediatrics. It highlights physiological variables that are abnormal for the age group by giving the variable a score and colour code. This allows attending staff to rely on the tool instead of carrying reference cards, or remembering ‘normal for age’ physiological variables. Colour bands are also key visual prompts that a physiological variable is worsening.

The benefit in using these scoring tools underpinned the decision to use a similar tool for collecting physiological data on the pilot study patients. A scoring tool would provide staff confidence in their decision making, especially as they would be caring for patients differently from usual practice (in using HFNC). In addition, as the MCH Executive were to
roll out the CEWT throughout the hospital in late 2011 – early 2012, it made sense to use this tool to collect relevant data from the study patients.

However, the CEWT does not capture FiO\textsubscript{2} or apparatus flow rate – only oxygen flow rate – hence, the tool was modified to incorporate these two factors. The name of the tool was changed to High Flow Oxygen Data (HiFOD). All other parameters remained unchanged from CEWT, and the HiFOD was printed in colour on A3 paper.

Education on using HiFOD, its components and actions, occurred in the months preceding the study, with 100% of nurses in the emergency department and paediatric ward planned to undergo training. Laminated cards were visibly displayed on all the study equipment and incorporated the use of HiFOD. Follow up education was also undertaken throughout the study period to mitigate any concerns over the use of the HiFOD form and the resultant scoring.

5.8.2.2 Other data collection tools and systems
A data collection tool was also developed to collect not only demographics but information such as prematurity, co-morbidities and respiratory virus identified from the nasopharyngeal aspirate (as reported on the hospital clinical laboratory interface: Kestral Computing Pty Ltd 1997–2013). Every patient’s admission and discharge times, and interhospital transfers, were able to be tracked from the hospital patient information system: iPM\textsuperscript{™} (CSC Version 1.86.5 Build 002). All PICU admissions were tracked and clinical information obtained from the PICU clinical information system (PiCIS\textsuperscript{™}, Spain). A screening log was kept of all potentially eligible patients during the study period. These patients were identified from the PED database: EDIS\textsuperscript{™} (iSOFT, Sydney, Australia).

Data for those patients who were not eligible (>12 months of age, and those not admitted to the ward), was logged. This screening log allowed potentially missed patients to be identified.

5.8.3 Pre-intervention preparations
Equipment for the study consisted of three ‘G’ sized medical air cylinders (BOC Limited, Australia) in PED areas with no piped air (Figure 5.2), and 5 HFNC set-ups consisting of:

- a humidification base (MR850, Fisher & Paykel Healthcare, Auckland, New Zealand)
- flow meter, 0–15 L capacity
• Bird® Air-Oxygen Blender (CareFusion, California, USA)
• air and oxygen hoses
• circuit (RT329, Fisher & Paykel Healthcare, Auckland, New Zealand)
• sterile water bag (Baxter Healthcare, Toongabbie, Australia).

All equipment was attached to a mobile pole (Figure 5.3).

5.8.4 Intervention procedure

Potential patients were screened in the PED and, if they met the inclusion criteria and if no exclusion criteria applied, the author was notified. Parents of eligible patients were then approached for consent and, if given, they were enrolled into the study. Ward staff were informed of the admission of a study patient.

Recruited patients were fitted with the appropriately sized nasal cannula to interface with the HFNC unit (BC2745 or BC3780, Fisher & Paykel Healthcare, Auckland, New Zealand) and this was secured with Fixomull® Stretch 10x10 (BSN Medical, Hamburg, Germany) tape to the face (Figure 5.4). Observations were recorded on the HiFOD form before starting HFNC treatment, and then at least hourly, as per hospital policy for managing a patient receiving oxygen therapy. Nasopharyngeal aspirates (sputum trap by ConvaTec Limited, Deeside, United Kingdom) were collected as soon as practicable, either in the
PED or the ward. A nasogastric tube (Argyle 6-8Fr, Covidien Healthcare, NSW, Australia) was inserted at the time of nasal cannula fitting to aid in decompressing the stomach, and if required for enteral feeding.

To initiate HFNC treatment, the FiO₂ was set to 0.6 on the blender, and the flow increased to 2 L/kg/min, or a maximum of 10 L/min over a few minutes. The FiO₂ was then decreased to maintain oxygen saturations of 94–98%. Oxygen saturation, heart rate and respiratory rate in the PED were monitored on the Infinity® Delta (Drager, Germany) (Figure 5.5) multiparameter monitor using a MasimoSET® LNOP® Inf-L SpO₂ adhesive sensor (Masimo, USA) (Figure 5.6). On the ward, the MasimoSET® Radical® (Masimo, USA) portable oxygen saturation monitor were used to monitor SpO₂ and heart rate (Figure 5.7). When the patient was ready to be admitted to the ward, two 'C' sized portable cylinders (medical oxygen, medical air, BOC Limited, Australia) were used during the patient transfer so that gas flow was maintained. The humidifier, however, was off during transfer as there was no battery back-up for this equipment. On arrival to the ward, the gas cables were transferred over to 'wall' piped medical oxygen and air, and the humidifier plugged into mains power and turned on.
A simplified study protocol instruction sheet was attached to each HFNC set-up, with a flow chart for both PED staff and for ward staff (Figure 5.8 and Figure 5.9). The protocol required oxygen saturations to be maintained at 94–98%, therefore if saturations were consistently >98%, the FiO₂ would be weaned. If saturations fell below 94%, then the FiO₂ would be increased. The aim was to wean oxygen to 21% (room air) with flow continuing. Once the patient's condition was stable, the flow would be turned off. If the patient then desaturated below 94%, flow would be reinstated at the previous flow rate, and if no improvement occurred, FiO₂ was to be increased until the desired SaO₂ of ≥94% was achieved. If, however, a FiO₂ of >0.6 was required, or there were apnoeic episodes, or if the bedside nurses had any concerns, then medical staff were to review the patient.

Infants were admitted to PICU on review by a paediatric consultant and PICU registrar/consultant. All other clinical management of infants with bronchiolitis remained as per hospital policy and paediatrician discretion. Pharmacological treatments remained as per treating physicians' orders. All clinical care, including positioning of the infants, remained as per normal ward management. Observations were to be collected on the HiFOD form until the infant was discharged from the ward.
Figure 5.8 – Flow chart for PED

Diagnosis Bronchiolitis

Eligible?

NO

Eligible?

NO

Call study staff for consent

YES

NO

Inclusion criteria
- \( O_2 \) requirement to keep SaO\(_2\) > 94%
- \( O_2 \) given via face mask or nasal prongs

Exclusion Criteria
- No oxygen requirement
- Home oxygen Tx for lung disease
- Upper airway obstruction
- Craniofacial malformation
- Severe respiratory distress requiring other means of support such as NIV/INV and PICU admission

Inclusion criteria
- \( O_2 \) requirement to keep SaO\(_2\) > 94%
- \( O_2 \) given via face mask or nasal prongs

IF:
- FiO\(_2\) > 60% needed to maintain SaO\(_2\) > 94%
- Score > 6
- Nurse concerns

Transfer to ward as per PED policy

Record obs on HiFOD Scoring Form. Frequency as per PED

Initiate HFNP
- 2 L/kg/min, max 10 L
- FiO\(_2\) 60%

Take Baseline Observations, with and without \( O_2 \) in situ

NOTIFY RMO AND TREAT AS CLINICALLY INDICATED
Figure 5.9 – Flow chart for ward

Patient arrives on ward from ED

Ensure equipment set up correctly, humidifier plugged in, set to ETT mode, water insitu

Record observations on HiFOD Scoring Form – frequency of observations as per ward policy

All clinical treatments and investigations as per ward policy

May be breast/bottle/nasogastrically fed as per standard ward practice

Adjustment of HFNP

1st – reduce FiO₂ to maintain SaO₂ between 94–98%

Avoid SaO₂ 100% for too long unless FiO₂ is 21%

When FiO₂ is 21%, turn flow OFF. The patient is now breathing room air.

Continue observations as per ward policy, document on HiFOD form.

IF RESPIRATORY DISTRESS RE-OCCURS AND SaO₂ DROPS <94%

Start flow at 2 L/kg/min to max 10 L/kg/min

If SaO₂ remains <94%, adjust FiO₂ till Sats 94–98 % achieved

If FiO₂ >60% required to maintain SaO₂ >94%, SEEK MEDICAL REVIEW

Notify medical officer if:-
- FiO₂ on blender >60%
- apnoeas
- need for SERT call
- concern of bedside nurse/TL about wellbeing of child

MEDICAL OFFICER TO MANAGE PATIENT AS CLINICALLY INDIACTED MAY NEED PICU ADMISSION
5.9 Sample size

While pilot study designs are often used to assess proposed procedures of an intervention, or to plan a larger study, preliminary pilot data may still be both statistically and clinically significant, even with small sample sizes.\textsuperscript{169,182,183} However, determining how many participants are required for a pilot study is somewhat nebulous. Depending on the outcomes and intention of a pilot, the sample size can range from 10–40 participants, and is often determined by cost and realistic time frames.\textsuperscript{183} When determining sample size for studies such as RCTs, it is necessary to consider the size in relation in the power required to detect the effect being considered. Determining sample size uses the concepts of standard error and confidence interval to quantify how many participants are included, and are often based on previous data or by carrying out a pilot study.\textsuperscript{184}

For this pilot study, determining the sample size required considering a number of factors. In previous RCTs investigating the role of bronchodilators or corticosteroids in bronchiolitis, approximately 400 patients needed to be recruited. This number was based on a treatment effect of reducing admission rates and LOS by 20%. The Mater Children's Hospital admits approximately 660 patients per year via the PED with bronchiolitis. Annual PICU admissions of patients with bronchiolitis (from PED, paediatric wards and externally\textsuperscript{166}) are about 140 patients. A study by Schibler et al\textsuperscript{15} and the success rate of HFNC treatment in the Mater Children's PICU indicated that a 10% reduction in PICU admission may be feasible. Therefore, enrolling 60 patients was deemed sufficient to demonstrate a reduction in the primary outcome (that is, admission to PICU) and inform both a sample size estimate, and clinical and admission criteria for the future RCT.

5.10 Blinding

Due to the nature of the study and the HFNC device, study staff were unable to be blinded.

5.11 Statistical methods

All data from a study patient's HiFOD forms was manually entered into Excel (Microsoft\textsuperscript{®} Excel 2010) spreadsheets. Data were then selected at set clinical points in time, namely: pre-oxygen use, post-oxygen (i.e. face/nasal cannula oxygen therapy, and at 1, 3, 6, 12, 24, and 48 hours post–HFNC), pre-PICU admission (if applicable), pre-HFNC cessation, and 4 hours post-HFNC cessation. These were entered into an Excel workbook which also included other demographic data, such as gender, age, prematurity, hospital LOS, PICU LOS, length of treatment (HFNC or standard oxygen treatment), respiratory
virus, co-morbidity, and any treatments such as antibiotics, salbutamol and steroids as collected on the data collection tool.

Following this, the data were imported into the statistical software program SPSS™ 15.0 (SPSS Inc., Chicago, IL). Data were manually checked for accuracy. Demographic and clinical data were compared between the expectant HFNC failure and success group using Fisher's exact test and independent T-test where appropriate. Mean and 95% confidence intervals (CI) were used for continuous variables with a parametric distribution. Median and interquartile range (IQR) were used for non-parametric variables. For the relationship between physiological data and time among the different patient groups, a generalised linear model (GLM) was used. To describe the change in physiological data over time between the groups, an analysis of variance (ANOVA) for repeated measurements with Bonferonni correction was used. In order to determine the sample size for a larger RCT, a power of 90% and type 1 error 0.05 will be adopted.

5.12 Ethical considerations

Children and young people are defined by the National Statement on Ethical Conduct in Human Research\(^\text{185}\) as a vulnerable population, and additional vigilance is required to ensure that they are protected in the conduct of studies. Ethical approval was sought from the Mater Health Services' Human and Research Ethics Committee (HREC) and the Medical Research Ethics Committee of The University of Queensland. All documentation for the Mater HREC was completed for the study and included:

- study protocol
- parent consent and information form (Appendix 2)
- staff information sheet
- simplified protocol sheet for the two departments
- budget proposal
- excerpt of PICU guidelines for high flow set-up
- CEWT tool (Appendix 3).

Parents were provided with a copy of the parent consent and information form, and participation was documented in the medical chart. All requirements for the Mater HREC were to be met during the study period, including annual and final reports, and data monitoring and safety committee (DMSC) reports. Any adverse events of deaths during
the study period were to be reported to the DMSC immediately, and could have resulted in early termination of the study due to safety considerations.

5.13 Storage of data collection sheets and electronic data

Data collection sheets, photocopied HiFOD forms and signed parental consent forms were stored in a locked cabinet, in a swipe card-accessed area of the PICU. Electronic files were stored on a password-protected computer located within this same area, on the Mater Hospital secured drive, and within a restricted folder.

5.14 A priori amendments to protocol

In the initial conception of the study, there were a number of elements that were considered and written into the protocol. These were: a randomised controlled trial design, inclusion criteria up to age 2 years (as bronchiolitis is most common up to this age), and conducted within two wards at MCH. In further consultation with key stakeholders, these elements were required to be amended (see Chapter 7.4.2.1) and the final protocol submitted for ethical approval consisted of a pilot study design, inclusion criteria to 12 months of age and conducted within one ward at MCH.

5.15 Other amendments to protocol and ethics

To fully describe the population cohort, recruitment monitoring in the initial five months of the study revealed that potentially eligible study participants were not being screened and identified for recruitment. Recognising the value of these patients as a comparison group, the protocol was amended for this group to be further assessed for eligibility. Potentially eligible patients were assessed and, if they met the study's enrolment criteria, their data were collected prospectively from medical records and entered into Excel workbooks at their point of entry into the study. The same inclusion and exclusion criteria used for the HFNC intervention patients were applied to this group.

Consequently, an amendment was obtained from Mater HREC to access the medical charts of this potential comparison group (Appendix 6). A waiver of consent was sought for this group, allowing the course of these patients (the comparison group) to be compared to the intervention (HFNC) group. The same statistical analysis techniques outlined in the protocol were applied to this group, and comparisons made between each group.
accordingly. Their details, such as date of birth and admitting ward, were noted on the screening log form, and subsequently transcribed into an Excel workbook.

5.16 Conclusion

This chapter has presented the protocol and methodology for the HFNC pilot study, including the study design and choice of physiological data collection tool. The protocol has been specified to the extent required for future replication studies. Additionally, the variation to the original design, which resulted in the inclusion of a comparison group, has been explained and detailed. The following chapter will present the results of this pilot study.
Chapter 6: Results

6.1 Introduction

In previous chapters the literature surrounding bronchiolitis and HFNC therapy have been described. The preceding chapter presented the methodology for the pilot study, and this chapter presents the results, including the resulting publication. Results are reported as consistent with the TREND guidelines. Before commencing the study, full ethical approval and governance considerations were obtained from both Mater HREC (Appendix 4) and the University of Queensland HREC (Appendix 5).

6.2 Participant flow

A total of 1111 patients were screened in the PED of the MCH, between July 2011 and May 2012. During that time, 94 patients satisfied the study's eligibility criteria and of those, 61 were consented and enrolled for HFNC treatment (intervention group). The remaining 33 eligible patients had not been approached for recruitment. They were identified and formed the comparison group who received standard treatment (Figure 6.1). Eighty-one patients were admitted who did not meet the inclusion criteria, that is, they had no oxygen requirement, had craniofacial malformations, had pre-existing home oxygen requirement or upper airway obstruction, or were commenced on oxygen therapy despite having oxygen saturations >94% on room air. These patients were excluded from the trial.
Figure 6.1 – Screening flow chart from the paediatric emergency department

6.3 Baseline data HFNC vs comparison group

6.3.1 Demographic data

Demographic data, specifically age and gender, were collected for each participant on admission, as summarised in Table 6.1. Gender was equally distributed between the groups with the HFNC group having 64% males and 36% females, and the comparison group having 58% males and 42% females. Ages were also similar with the mean [95% CI] for the HFNC group 157 days [128–187] and the comparison group 146 days [104–188].
6.3.2 **Clinical data**

Clinical data collected for each participant comprised weight, prematurity and co-morbidity. Weight was comparable between the two groups with mean [95%CI] of the HFNC group at 6.8 kg [6.1–7.5] and the comparison group at 6.6 kg [5.6–7.7]. Prematurity was described as gestation of less than 37 completed weeks, with 31% premature in the HFNC group and 18% in the comparison group. Co-morbidities encompassed infants with Trisomy 21, tracheomalacia, and repaired/unrepaired cardiac anomalies – 5% in the HFNC group and 6% in the comparison group had these conditions. No statistical differences were identified on any of these characteristics between the HFNC and comparison groups (Table 6.1).

6.3.3 **Physiological data**

Physiological assessment of heart rate, respiratory rate, oxygen saturation (SpO₂) and HiFOD score did not differ significantly between groups on admission. The mean [95% CI] heart rate for the HFNC group on admission was 158 bpm [153–163] and 159 bpm [152–166] in the comparison group. Mean respiratory rate was also comparable, being 54 rpm [51–57] in the HFNC group and 53 rpm [50–57] in the comparison group. The admission SpO₂ was almost identical with the HFNC group mean 89% [88–90] and the comparison group 90% [89–92]. Finally, the mean HiFOD score in the HFNC group was 6 [5–8] with the comparison group being 5.5 [4–7] (Table 6.1).

Nasopharyngeal aspirates revealed respiratory viruses, namely: respiratory syncytial virus (RSV), influenza, rhino/enterovirus, adenovirus, human metapneumovirus (HMPV), or combinations of these. The most predominant single viral infection was RSV (48%) (Figure 6.2) and overall, 60% of viral infections incorporated RSV. There were no statistically significant differences between the two groups in rate of respiratory infection as determined by nasopharyngeal aspirate, p=0.54.

Day of illness (the number of days the participant was ill prior to PED presentation) was also not statistically different between the groups, with the HFNC group presenting at a mean [95%CI] of 3.0 days [1–5] and the comparison group at 2.9 days [2–3.5].

6.3.4 **Treatment data**

Treatment modalities such as steroid use (12% each group), salbutamol nebulisers (26% and 24%) or antibiotics (20% and 24%) likewise did not exhibit statistically significant differences between the HFNC group and comparison group respectively.
6.3.5 **Length of stay**

The hospital length of stay was calculated as a median with interquartile ranges, and was almost identical between the groups. The HFNC group was 92 hours (59–141) and the comparison group 92 hours (48–124), p=0.56.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Variable</th>
<th>HFNC Group n=61</th>
<th>Comparison Group n=33</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Male</td>
<td>39 (64%)</td>
<td>19 (58%)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>22 (36%)</td>
<td>14 (42%)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Age (days)</td>
<td>157 [128–187]</td>
<td>146 [104–188]</td>
<td>0.66</td>
</tr>
<tr>
<td>Physiological</td>
<td>Weight (kg)</td>
<td>6.8 [6.1–7.5]</td>
<td>6.6 [5.6–7.7]</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Ex-prematurity</td>
<td>19 (31%)</td>
<td>6 (18%)</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Other co-morbidity</td>
<td>3 (5%)</td>
<td>2 (6%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Clinical</td>
<td>Heart rate (bpm)</td>
<td>158 [153–163]</td>
<td>159 [152–166]</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate (rpm)</td>
<td>54 [51–57]</td>
<td>53 [50–57]</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>SpO2 (%)</td>
<td>89 [88–90]</td>
<td>90 [89–92]</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>HiFOD Score</td>
<td>6 [5–8]</td>
<td>5.5 [4–7]</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>NPA positive</td>
<td>55 (95%)</td>
<td>32 (97%)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>Day of Illness</td>
<td>3.0 [1–5]</td>
<td>2.9 [2–3.5]</td>
<td>0.68</td>
</tr>
<tr>
<td>Treatment</td>
<td>Steroids (Tx)</td>
<td>7 (12%)</td>
<td>4 (12%)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Salbutamol (Tx)</td>
<td>16 (26%)</td>
<td>8 (24%)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Antibiotics (Tx)</td>
<td>12 (20%)</td>
<td>8 (24%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
6.4 Primary outcome

The primary outcome measure was admission to the PICU. Within each group, those admitted to PICU were classified as Non-Responders, with those managed successfully on the ward classified as Responders.

Of the 61 patients in the HFNC group, 8 (13%) were admitted to the PICU and therefore labelled HFNC Non-Responders. This is compared to 53 (87%) who remained on the paediatric ward and labelled HFNC Responders. In the comparison group, 10 (31%) required PICU admission (comparison Non-Responders) and 23 (69%) remained on the paediatric ward (comparison Responders). When compared, those in the intervention group (HFNC) were significantly less likely to be admitted to PICU than those in the comparison group [OR 4.086, 95% CI 1.0–8.2, p=0.04].

6.4.1 Demographic and physiological characteristics of Responders vs Non-Responders on admission

Further analysis was necessary to determine whether there were differences in demographic or physiological characteristics at admission between the Non-Responders and Responders that may have unduly skewed the outcome (Table 6.2). Demographic data were not statistically significant between the Non-Responders and Responders of each group. Mean [95% CI] for Non-Responders (HFNC and comparison) for age (in days) were 170 [70–270] and 115 [40–190], and for Responders (HFNC and comparison) 157
Weight (in kg) was also similar between each Non-Responder and Responder group.

No differences were found in percentages of premature infants (12% and 10% in the Non-Responders (HFNC and comparison); 34% and 22% in the Responders (HFNC and comparison)) or those with co-morbidities (12% and 20%; 4% and 0% respectively).

### 6.4.2 Clinical characteristics of Responders vs Non-Responders on admission

Differences in physiological data (heart rate, respiratory rate, SpO2, and HiFOD score) were not statistically significant. On admission, the mean [95% CI] heart rate of the Non-Responders were 159 bpm [142–176], 161 bpm [171–151], HFNC and comparison group, respectively. The Responders were 157 bpm [151–163], 159 bpm [151–167], HFNC and comparison group, respectively. Admission mean respiratory rate for the Non-Responders was 54 rpm [47–61], 58 rpm [53–63], HFNC and comparison respectively. The Responders group was 54 rpm [51–57], 52 rpm [48–56], HFNC and comparison respectively. The SpO2 for the Non-Responders on admission was 88% [86–92], 91% [85–94], HFNC and comparison respectively. The Responders also had very similar SpO2, 89% [88–90], 90% [89–91]. Finally, the HiFOD score was almost identical between the Non-Responders, 7 [6–8], 7 [6–8.5], and within the Responders groups, 6 [4–8], 5 [4–7], HFNC and comparison respectively.

Infection with a respiratory virus was also not statistically significant between any of the groups. Non-Responders had 87% and 90% (HFNC and comparison) infections, with Responders 90% and 100%. RSV continued to be the most prevalent cause of respiratory viral infection amongst all the groups, attributable to 75% and 80% of infections in the Non-Responders (HFNC and comparison; Figure 6.3 and Figure 6.4), and 52% and 61% in the Responders (Figure 6.5 and Figure 6.6).

Day of illness on admission was also not statistically significant between any of the groups. Non-Responders presented on day 3.0 [2–4] and 2.5 [2–3] and Responders on day 3 [2.5–3.5] and 3 [2–4].
6.4.3 Length of treatment

The length of treatment (in hours) of either HFNC or oxygen therapy between the Non-Responders and Responders was not statistically significant. Median (with interquartile ranges) for the Non-Responders was 7 hours (4.5–12) for the HFNC group and 4 hours (2–7) for the comparison group before they were admitted to PICU, p=0.07. For the Responders, it was 53 hours (26–101) for the HFNC group, 40 hours (24–63) for the comparison group, p=0.32.
Table 6.2 – Demographic, physiological and clinical characteristics of Responders and Non-Responders in HFNC and comparison groups at admission

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Variable</th>
<th>HFNC Non-Responders n=8</th>
<th>Comparison Non-Responders n=10</th>
<th>p value</th>
<th>HFNC Responders n=53</th>
<th>Comparison Responders n=23</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Age (days)</td>
<td>170 [70–270]</td>
<td>115 [40–190]</td>
<td>0.34</td>
<td>157 [121–186]</td>
<td>160 [111–206]</td>
<td>0.77</td>
</tr>
<tr>
<td>Physiological</td>
<td>Weight (kg)</td>
<td>6.9 [4.8–9.0]</td>
<td>6.3 [4.0–8.6]</td>
<td>0.70</td>
<td>6.7 [(5.9–7.4]</td>
<td>6.6 [5.7–7.8]</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Ex-prematurity</td>
<td>1 (12%)</td>
<td>1 (10%)</td>
<td>0.26</td>
<td>18 (34%)</td>
<td>5 (22%)</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Other co-morbidity</td>
<td>1 (12%)</td>
<td>2 (20%)</td>
<td>0.08</td>
<td>2 (4%)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Clinical</td>
<td>Heart Rate (bpm)</td>
<td>159 [142–176]</td>
<td>161 [171–151]</td>
<td>0.98</td>
<td>157 [151–163]</td>
<td>159 [151–167]</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Respiratory Rate (rpm)</td>
<td>54 [47–61]</td>
<td>58 [53–63]</td>
<td>0.66</td>
<td>54 [(51–57]</td>
<td>52 [48–56]</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>SpO2 (%)</td>
<td>88 [86–92]</td>
<td>91 [85–94]</td>
<td>0.39</td>
<td>89 [88–90]</td>
<td>90 [89–91]</td>
<td>0.17</td>
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<td></td>
<td>HiFOD Score</td>
<td>7 [6–8]</td>
<td>7 [6–8.5]</td>
<td>0.60</td>
<td>6 [4–8]</td>
<td>5 [4–7]</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>NPA Positive</td>
<td>7 (87%)</td>
<td>9 (90%)</td>
<td>0.47</td>
<td>43 (90%)</td>
<td>23 (100%)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Day of Illness</td>
<td>3.0 [2–4]</td>
<td>2.5 [2–3]</td>
<td>0.42</td>
<td>3 [2.5–3.5]</td>
<td>3 [2–4]</td>
<td>0.68</td>
</tr>
</tbody>
</table>
6.5 Secondary outcomes

Secondary outcome measures encompassed physiological parameters such as respiratory and heart rate, and the overall HiFOD score. Other outcome measures comprised adverse events, which include bradycardia, pneumothorax, cardiopulmonary arrest and emergency intubation; and for those patients admitted to PICU, non-invasive ventilation and/or intubation.

6.5.1 Physiological parameters

A GLM was used to analyse differences in heart rate, respiratory rate and HiFOD score over time. ANOVA was used to determine the difference between the means of the groups, with the p-value set at <0.05 for significance. Responders to therapy, whether in the HFNC group or undergoing standard treatment, had clinically significant differences at 60 minutes post-initiation of intervention/standard treatment compared to Non-Responders (Table 6.3 & 6.4). Responders to HFNC showed a reduction of 15–20% in the baseline heart rate on admission, otherwise quantified as a reduction in heart rate of 15 bpm.

| Table 6.3 – Clinical parameters of HFNC group at 60 minutes of treatment |
|--------------------------|--------------------------|--------------------------|
|                         | Responders n= 53 mean [95%CI] | Non-Responders n= 8 mean [95%CI] | p-value |
|Heart rate (bpm)         | 144 [138–150]              | 162 [152–171]              | 0.02    |
|Respiratory rate (rpm)   | 51 [48–54]                 | 58 [48–69]                 | 0.07    |
|HiFOD score              | 4.5 [4–5.5]                | 6.5 [5–8]                  | 0.006   |

| Table 6.4 – Clinical parameters of comparison group at 60 minutes of treatment |
|--------------------------|--------------------------|--------------------------|
|                         | Responders n= 23 mean [95%CI] | Non-Responders n= 10 mean [95%CI] | p-value |
|Heart rate (bpm)         | 141 [131–150]              | 160 [136–183]              | 0.06    |
|Respiratory rate (rpm)   | 45 [41–49]                 | 51 [44–45]                 | 0.16    |
|HiFOD score              | 3 [2–4]                    | 6.5 [5–8]                  | 0.00    |
6.5.1.1 Heart rate

Overall between the four groups there was a significant difference in heart rate over time from admission, p<0.001 (Figure 6.7). Heart rate in infants remaining in the paediatric ward (Responders) for both HFNC group and comparison group dropped significantly within the first 60 minutes. In infants requiring PICU admission (Non-Responders) heart rate either remained unchanged or increased after admission. The heart rates for Responders in the HFNC group reduced significantly (p=0.02) within 60 minutes from a mean [95% CI] of 157 bpm [151–163] to 144 bpm [138–150] whereas the heart rate of the Non-Responders increased slightly from 159 bpm [142–176] to 162 bpm [152–171].

![Heart rate chart](image)

*Figure 6.7 – Change in heart rate in intervention and comparison groups after inclusion in the study*

6.5.1.2 Respiratory rate

Between the four groups there was also a significant difference in respiratory rate over time from admission, p=0.05 (Figure 6.8). The respiratory rate in the HFNC Non-Responders group remained high but in the comparison Non-Responders group decreased after admission. At 60 minutes, the Responders in the HFNC group dropped their respiratory rate from a mean [95% CI] of 54 rpm [51–57] to 51 rpm [48–54] with the Non-Responders increasing from 54 rpm [47–61] to 58 rpm [48–69], p=0.07. While the
differences were not statistically significant at 60 minutes, they were statistically and clinically significant at 180 minutes post-treatment initiation, p<0.05.

![Graph showing change of respiratory rate in intervention and comparison group after inclusion in the study](image)

**Figure 6.8 – Change of respiratory rate in intervention and comparison group after inclusion in the study**

### 6.5.1.3 HiFOD score

The HiFOD score as a composite of physiological data changed significantly between the groups after admission, p< 0.001 (Figure 6.9). HiFOD score decreased for the HFNC Responders and comparison Responders significantly 60 minutes after admission, but remained high in infants requiring PICU admission. The Responders in the HFNC group dropped their HiFOD score from a mean [95% CI] of 6 [4–8] to 4.5 [4–5.5], with the Non-Responders slightly decreasing their HiFOD score from 7 [6–8] to 6.5 [5–8] at 60 minutes.
6.5.1.4 Post-hoc analysis – Physiological data

Receiver operator characteristic (ROC) curves are usually applied in diagnostic statistics. This analytical procedure uses sensitivity and specificity to determine the likelihood of having or not having a particular disease.\textsuperscript{184} Logically, this same test can be applied to predictors of physiological parameters to determine the sensitivity and specificity for predicting treatment failure.

Area under the curve ROC (AUROC) was applied to heart rate, respiratory rate and HiFOD score and were found to be statistically significant in the HFNC group to predict PICU admission, $p<0.001$ (Figure 6.10). The sensitivity of heart rate to predicting PICU admission was $0.74$ [95% CI 0.66–0.83]. Respiratory rate was also sensitive, $0.73$ [95% CI 0.65–0.81], as was HiFOD score, $0.80$ [95% CI 0.73–0.88].
6.5.2 Adverse events

No serious adverse events (such as bradycardia, pneumothorax, cardiopulmonary arrest or need for emergency intubation) occurred during the study in either the HFNC group or through retrospective chart audit in the comparison group.

6.5.3 PICU clinical course

Of those infants admitted to PICU (n= 18), one infant in the HFNC group and three in the comparison group required a period of non-invasive ventilation (NIV). Within the PICU, NIV is given via an appropriately fitting face mask using the Evita®XL ventilator (Drager, Germany) in pressure support mode. The remaining infants admitted to PICU received HFNC treatment at 2 L/kg/min. None of the infants required intubation in the PICU.

6.5.4 Post-hoc outcomes

A further aim was to determine a sample size for a multicentre RCT. Under consultation with a statistician, with the power set at 90% and type 1 error of 0.05, based on PICU admission rates of 13% for HFNC therapy group and 33% for standard therapy group,
there would need to be 121 participants in each group. However, it is feasible that a 10% reduction in PICU admission rate is achievable. Therefore 392 participants in group one (standard therapy) and 392 in group two (HFNC therapy) achieves 90% power to detect an absolute difference between the group proportions of 10%. The proportion of participants admitted to PICU in the HFNC group is assumed to be 30% under the null hypothesis and 20% under the alternative hypothesis. The proportion in the standard therapy group is 30%. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test is targeted at 0.05.

Although the study did not intend to consider feeding in the initial analysis and outcome measures, it emerged to be an issue worthy of exploring. Post-hoc analysis of feeding in the HFNC patients during the study revealed they were fed via nasogastric tube, orally or intravenous infusion, or a combination of these (Figure 6.8). No orally fed HFNC patient was admitted to PICU. Those admitted to PICU (Non-Responders) were either nasogastric fed or had fluids delivered via intravenous infusion (Table 6.5). There were no reports of adverse events such as abdominal overdistention, nasal trauma or aspiration from oral feeds.

![Figure 6.11 – Feeding mode in HFNC patients](image)
Table 6.5 – Feeding mode in HFNC Responders and Non-Responders

<table>
<thead>
<tr>
<th>Mode of feeding</th>
<th>HFNC Responders n=53</th>
<th>HFNC Non-Responders n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral only</td>
<td>21 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Nasogastric (NG) only</td>
<td>13 (24%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Combination NG/Oral</td>
<td>19 (36%)</td>
<td>0</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0</td>
<td>2 (25%)</td>
</tr>
</tbody>
</table>

P=0.000

Infant positioning was not recorded formally during the study period nor collected on the comparison group. However, the study protocol did not stipulate any particular way to position the patient. This was left to standard ward protocol for managing infants with bronchiolitis. It is likely that there was no difference in the way infants were positioned between the HFNC group and comparison group, however no data exists to support this.

6.6 Summary

This chapter detailed the findings of the pilot study. The key results from instituting HFNC in a ward setting suggest that: PICU admissions may be significantly reduced; physiological parameters such as heart rate, respiratory rate and HiFOD score (as a composite of physiological variables) could be used, either singularly or combined, to determine potential PICU admission; instituting HFNC therapy following this protocol was feasible and gave a reasonable indication of success within 60 minutes of commencement; factors such as age, weight, gender, prematurity and co-morbidity did not play a significant role in predicting treatment failure; use of HFNC therapy did not increase hospital length of stay; and there was no apparent association between oral feeding whilst on HFNC and admission to PICU.

The following chapters will discuss the results and what they may mean for clinicians, elaborate on the limitations to the study and thesis, and explore further areas of investigation.

6.7 Publication
Aim: To obtain data on the safety and clinical impact of managing infants with bronchiolitis on the ward with high-flow nasal cannula (HFNC) treatment.

Methods: A prospective pilot study was conducted of 61 infants aged <12 months with bronchiolitis and oxygen requirement presenting to the emergency department. HFNC was commenced at 2 L/kg/min, and fraction of inspired oxygen was titrated to oxygen saturation > 94%. A standard-treatment group (n = 33) managed with standard low-flow subnasal oxygen during the same time period was retrospectively identified.

Results: Admission demographics, heart rate (HR) and respiratory rate (RR) were similar in test and standard-treatment groups. Responders and non-responders to HFNC were identified within 60 min of treatment. Non-responders to HFNC requiring paediatric intensive care unit (PICU) admission showed no change in HR and RR, whereas responders showed decreases in HR and RR (*P* < 0.02). Patients receiving HFNC were four times less likely to need PICU admission than the standard treatment group (OR 4.086, 95%CI 1.0–8.2; *P* = 0.043). No adverse events such as pneumothorax, bradycardia, bradypnoea, emergency intubation or cardiopulmonary resuscitation were observed. No patients admitted to the PICU required intubation.

Conclusions: HFNC treatment in the paediatric ward is safe. Non-responders requiring PICU admission can be identified within the first hour of HFNC treatment by monitoring HR and RR. It is feasible to undertake a randomised controlled trial based on this pilot with the aim of decreasing PICU admissions.

Key words: bronchiolitis; high-flow nasal cannula; infant.
randomised controlled trial (RCT) and to present data on the decreased prevalence of respiratory deterioration and requirement for PICU admission.

Methods

Study design

A prospective pilot study was conducted, investigating the use of HFNC treatment in a paediatric ward setting. The use of an RCT design for this study was denied by the institutional ethics board, as there are no convincing data yet available for safety of HFNC use in regular ward settings. Inclusion of case controls who were admitted during the same period was retrospectively allowed by the ethics board for the purpose of comparison. These patients received standard oxygen therapy and are referred to as the standard-treatment group.

Study protocol

Prior to the study, staff education on the protocol and equipment was implemented utilising a structured education plan. The plan targeted both medical and nursing staff in the emergency department (ED) and paediatric ward. ED staff education focused on recognition and identification of candidates meeting inclusion and exclusion criteria, adherence to study protocol, notification to study investigator, understanding correct selection and application of equipment, commencement of HFNC treatment and ongoing assessment of the patient. Ward staff education focused on ongoing respiratory care, adherence to the study protocol, and understanding and recognition of deteriorating and improving infants.

Patients were screened from July 2011 to May 2012 in the ED of Mater Children’s Hospital, Brisbane, Queensland, Australia, for the following inclusion criteria: age <12 months, clinical diagnosis of bronchiolitis and oxygen requirement ($S_pO_2 < 94\%$ in room air). Exclusion criteria were the following: craniofacial malformation, upper airway obstruction (stridor), and impending PICU admission based on severity of illness (impending intubation, NIV, low level of consciousness, apnoea) or transfer elsewhere. Informed consent to the study was obtained for all patients receiving HFNC treatment.

Patients for the standard-treatment group were identified retrospectively through chart review and included all infants with the same inclusion and exclusion criteria as the study patients who were admitted during the same time period to the same paediatric ward. Informed consent was waived for this group.

HFNC intervention

After consent was provided by the parents or guardians, the infants had the appropriate-sized nasal cannula applied, and flow was commenced through a circuit (RT329, BC3780 and BC2745; Fisher & Paykel Healthcare, Auckland, New Zealand) at 2 L/kg/min to a maximum of 10 L/min. Fraction of inspired oxygen ($F_{O_2}$) was titrated (Bird Air–Oxygen Blender, CareFusion, Yorba Linda, CA, USA) to maintain oxygen saturation between 94% and 98%, and the humidifier (Fisher & Paykel Healthcare MR880) was auto-set at 37°C. All other areas of nursing and medical management for bronchiolitis remained unchanged for the study purpose according to standard hospital protocol and consultant directive. Patients were transferred to the paediatric ward after commencement of HFNC treatment. Once $F_{O_2}$ could be reduced to 0.21, and oxygen saturations remained at 94% or higher, flow was turned off. If $S_pO_2$ dropped below 94%, flow returned at the same rate. If $S_pO_2$ did not improve, then $F_{O_2}$ was increased and titrated to achieve $S_pO_2$ of 94% or higher. This weaning procedure was repeated until the patient was able to remain off HFNC treatment.

Measures

Physiological parameters including heart rate (HR), respiratory rate (RR), $S_pO_2$, temperature and a respiratory score for WOB were documented (from no distress to severe distress in three levels). Observations were recorded on admission and at regular time points until discharge. Hospital length of stay (LOS) and length of treatment (LOT) of either HFNC treatment or low-flow subnasal oxygen treatment were measured. Demographic data and comorbidities such as prematurity, chromosomal abnormality and repaired/unrepaired cardiac anomaly were recorded. Serious adverse events, as a measure of safety, were defined as cardiopulmonary arrest, pneumothorax, bradypnoea, bradycardia, requirement for CPR or emergency intubation in the ward/PICU. Criteria for admission to PICU were the following: requirement for escalation of care, including cases of $S_pO_2 < 92\%$ despite 2 L/min $O_2$ in the control group or $F_{O_2} > 60\%$ in the HFNC group; inability to manage the patient on the ward (nursing); and deterioration in physiological parameters (persistent tachypnoea (>60 breaths/min) and tachycardia (>180 beats/min)). PICU admission in such cases was discussed and determined between the paediatric consultant and PICU registrar/consultant after patient review.

Statistical analysis

Demographic and clinical data, the number of adverse events and the number of PICU admissions were compared between the HFNC and standard-treatment groups using Fisher’s exact test and the independent-samples $t$-test where appropriate. For the relationship between physiological data and time among the different groups, a generalised linear model (GLM) was used. To describe the change of physiological data over time, an ANOVA for repeated measurements with Bonferroni correction was used (SPSS 15.0, SPSS Inc, Chicago, IL, USA). Data are presented as mean and 95% confidence interval (CI), and a $p$ value < 0.05 was considered significant.

Results

A total of 1111 patients were screened in the ED between July 2011 and May 2012, and 61 patients were enrolled for HFNC treatment. Subsequently, 33 patients were identified retrospectively as meeting the inclusion criteria and included in the standard-treatment group (Fig. 1). There were no statistically significant differences in the demographic and physiological characteristics of patients in the HFNC and standard-treatment groups on admission (Table 1).
There were no serious adverse events observed during the study in either group, and importantly, no emergency procedures such as intubation and mechanical ventilation were required.

Overall, among the four patient groups, there was a significant difference in the change of HR over time ($P < 0.001$, GLM) from admission (Fig. 2). The HR in patients remaining in the paediatric ward for both HFNC and standard-treatment groups dropped significantly within the first 60 min (responders). In patients requiring PICU admission, the HR remained unchanged and even increased after admission (non-responders). Responders to care could be identified by their HR dropping by 15 beats (or 15–20%) from their baseline at admission.

**HFNC Responders (managed on ward)**

- **n = 53**
- Mean HR changed significantly within 60 min from 158 beats/min (95% CI 154–164) to 144 beats/min (95% CI 138–150), whereas the mean HR of the non-responders increased slightly from 159 beats/min (95% CI 144–173) to 162 beats/min (95% CI 152–171) ($P = 0.02$).

**HFNC Non-responders (required PICU admission)**

- **n = 8**

**Standard-treatment Responders (managed on ward)**

- **n = 23**

**Standard-treatment Non-responders (required PICU admission)**

- **n = 10**

**Table 1** Demographic and physiological characteristics of high-flow nasal cannula and standard-treatment groups at admission

<table>
<thead>
<tr>
<th></th>
<th>HFNC group ($n = 61$)</th>
<th>Standard-treatment group ($n = 33$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, $n$ (%)</td>
<td>39 (64)</td>
<td>19 (58)</td>
<td>0.66</td>
</tr>
<tr>
<td>Female, $n$ (%)</td>
<td>22 (36)</td>
<td>14 (42)</td>
<td>0.66</td>
</tr>
<tr>
<td>Age (days), mean (95% CI)</td>
<td>157 (128–187)</td>
<td>146 (104–188)</td>
<td>0.66</td>
</tr>
<tr>
<td>Weight (kg), mean (95% CI)</td>
<td>6.8 (6.1–7.5)</td>
<td>6.6 (5.6–7.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Ex-prematurity (&lt;37 weeks gestation), $n$ (%)</td>
<td>19 (31)</td>
<td>6 (18)</td>
<td>0.23</td>
</tr>
<tr>
<td>Other comorbidity, $n$ (%)†</td>
<td>3 (5)</td>
<td>2 (6)</td>
<td>0.58</td>
</tr>
<tr>
<td>NPA-positive, $n$ (%)‡</td>
<td>55 (95)</td>
<td>32 (97)</td>
<td>0.54</td>
</tr>
<tr>
<td>Heart rate (beats/min), mean (95% CI)</td>
<td>158 (153–163)</td>
<td>159 (152–166)</td>
<td>0.75</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min), mean (95% CI)</td>
<td>54 (51–57)</td>
<td>53 (50–57)</td>
<td>0.78</td>
</tr>
<tr>
<td>$S_O_2$, (%)</td>
<td>89 (88–90)</td>
<td>90 (89–92)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospital length of stay (h), median (IQR)</td>
<td>92 (59–141)</td>
<td>92 (48–124)</td>
<td>0.60</td>
</tr>
<tr>
<td>S Albutamol therapy, $n$ (%)</td>
<td>16 (26)</td>
<td>8 (24)</td>
<td>0.83</td>
</tr>
<tr>
<td>Steroid therapy, $n$ (%)</td>
<td>7 (12)</td>
<td>4 (12)</td>
<td>0.93</td>
</tr>
<tr>
<td>Antibiotic therapy, $n$ (%)</td>
<td>12 (20)</td>
<td>8 (24)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

†Includes trisomy 21, repaired and unrepaired cardiac anomaly, and tracheomalacia. ‡Viruses including respiratory syncytial virus, influenza, rhinovirus, enterovirus, adenovirus and human metapneumovirus. Fisher’s exact test and independent-samples $t$-test have been used as appropriate. CI, confidence interval; HFNC, high-flow nasal cannula; NPA, nasopharyngeal aspirate.

Fig. 1 Screening flow chart from the emergency department (ED). †Patients were eligible but not approached, as ED staff did not alert study staff. HFNC, high-flow nasal cannula; PICU, paediatric intensive care unit.
similarly, the change in RR after admission was significantly different between the groups over time ($P = 0.05$, GLM) (Fig. 5). The RR decreased significantly for both the HFNC responders and the standard-treatment responders after admission. The RR in the HFNC non-responder group remained high, but in the standard-treatment non-responders it decreased after admission. In the responders in the HFNC group, RR dropped from 54 breaths/min (95% CI 51–57) to 51 breaths/min (95% CI 48–54), with that of the non-responders increasing from 54 breaths/min (95% CI 48–60) to 58 breaths/min (95% CI 48–69) ($P = 0.07$) at 60 min. however, the differences in RR became significant at 180 min ($P < 0.05$).

Of the 61 patients in the HFNC group, 8 (13%) were admitted to the PICU (HFNC non-responders) compared with 53 (87%) who remained on the paediatric ward (HFNC responders). In the standard-treatment group, 10 patients (31%) required PICU admission (standard-treatment non-responders), and 23 (69%) remained on the paediatric ward (standard-treatment responders) (OR 4.086, 95% CI 1.0–8.2; $P = 0.043$). Between the responders and non-responders in both groups (HFNC and standard treatment) there were no physiological and demographic differences on admission (Table 2). Of those patients admitted to the PICU, one patient in the HFNC group and three in the standard-treatment group required a period of NIV. The remaining patients referred to the PICU received HFNC treatment only at 2 L/kg/min. No patients were intubated.

Hospital LOS was similar between the two groups ($P = 0.56$), with the median time being 92 h for both the HFNC and standard-treatment groups (95% CI 52–140). LOT was similar for patients admitted to the PICU and those who remained on the paediatric ward in the standard-treatment group as well as the HFNC group ($P = 0.07$ and $P = 0.32$, respectively).

Discussion

The data from our study show that HFNC treatment can safely be used in a regular paediatric ward with a 1:4 nursing ratio, as no serious adverse event was observed. We determined that the safety of HFNC treatment can be monitored using clinical indicators such as HR and RR, providing a safe boundary for HFNC use in the ward. Responders and non-responders to HFNC treatment can be identified and described using HR and RR within 60 min of application. It is reasonable to anticipate that a future larger RCT may make similar findings of reduced PICU admission rates (4 times less likely) by following our protocol.

This pilot study was tested in a ‘real-world’ environment where standard care was not changed, only the oxygen delivery device. This approach allowed separation of oxygen delivery-specific aspects of the treatment and identification of responders and non-responders, which was important to demonstrate as a safety aspect of HFNC treatment. Infants responding to HFNC treatment showed decreased HR within the first hour of initiation. The RR also dropped in the responders, but with a slight delay at 180 min. The non-responders to HFNC showed no change in HR and RR within the first 60 min of observation. Non-responders to HFNC may warrant medical review for potential PICU admission. A similar pattern was also observed in the standard-treatment group, in which responders and non-responders to standard treatment could be identified within 60 min. Interestingly, in the standard-treatment group the RR in the non-responders dropped within the first 60 min compared with the responders, but the differences were not statistically significant. This drop in RR may have been due to a mild degree of hypoxaemia or may be explainable by the low number of patients in the study. This concept of certain parameters differentiating responders from non-responders has been identified in other studies. One limitation of the study design is that the repeated measurement of HR and RR were robust descriptors but not necessarily predictors of response or non-response for both the intervention and comparison groups. Real predictors such as prematurity, heart disease and pre-existing hospitalisation could be identified within 60 min. Interestingly, in the standard-treatment group the RR in the non-responders dropped within the first 60 min compared with the responders, but the differences were not statistically significant. This drop in RR may have been due to a mild degree of hypoxaemia or may be explainable by the low number of patients in the study. This concept of certain parameters differentiating responders from non-responders has been identified in other studies. One limitation of the study design is that the repeated measurement of HR and RR were robust descriptors but not necessarily predictors of response or non-response for both the intervention and comparison groups. Real predictors such as prematurity, heart disease and pre-existing hospitalisation could be identified within 60 min.
Table 2 Demographic and physiological characteristics of responders and non-responders in high flow nasal cannula and standard treatment groups at admission

<table>
<thead>
<tr>
<th></th>
<th>High-flow nasal cannula responders (n = 23)</th>
<th>Standard treatment responders (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days), mean (SD)</td>
<td>170 (70–270)</td>
<td>6.9 (10–14)</td>
<td>0.34</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>4.3 (1.8–9.0)</td>
<td>2.0 (1.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Respiratory rate (bpm), mean (SD)</td>
<td>64 (39–120)</td>
<td>7.5 (12–61)</td>
<td>0.13</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>88 (86–92)</td>
<td>7.5 (6.5–12)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Includes trisomy 21, repaired and unrepaired cardiac anomaly, and tracheomalacia. Viruses including respiratory syncytial virus, influenza, rhinovirus, rhinovirus, enterovirus, adenovirus and human metapneumovirus.

No patients subsequently admitted to the PICU needed intubation, and all continued either on HFNC or NIV. This low intubation rate is consistent with our and others’ previously reported use of HFNC in bronchiolitis. The early use of HFNC in a paediatric ward reduced the number of PICU admissions without any serious adverse events having been observed. We speculate that the early application of HFNC treatment is the key element, preventing further progression of airway obstruction and reversing some of the atelectasis. A recent uncontrolled study comparing HFNC with nasal CPAP showed that HFNC may be associated with a similar efficacy and even a trend towards a reduction in need for sedation. This experience is aligned with the trend towards use of early NIV in general. However, HFNC treatment did not shorten hospital LOS overall, and its associated physiological effect does not modulate the course of the underlying viral illness.

While hospital LOS was not shortened during the study, there are fiscal implications for reducing PICU admissions. The current cost for a 92-h combined PICU and ward admission in our hospital is estimated at A$15,517 per patient. The costs for the same patient on the paediatric ward are estimated at A$4,992 per patient. It is predicted that the annual cost saving for our 19-bed PICU with 1,400 admissions annually would be approximately A$1.2 million.

For a future RCT, the definition of high flow needs to be discussed. The original idea of delivering higher flow rates at >2 L/min originated from a need for better humidification of the delivered oxygen. In the past, this was achieved using higher flow rates. These higher flow rates created inadvertent CPAP. Previously published papers have explained some of the physiological effect of high flow with inadvertent CPAP. A study by Milesi et al. showed that flow rates of approximately 1.5–2 L/kg/min created a positive pharyngeal pressure during the entire respiratory cycle. Interestingly, a recent study by Mundel et al. in healthy adults has shown that during the inspiratory phase little or no positive pressure is delivered, and only during the expiratory phase is positive pressure observed. Further detailed physiological studies measuring changes on high flow, particularly of the intrathoracic pressures, are needed.

Generally, flow rates > 2 L/min subnasally in infants are regarded as ‘high flows’ with a maximal limit of 8–10 L/min. This maximum of 10 L/min using our HFNC device was not based on any clinical or physiological rationale but solely on the decision of the device manufacturer. For this study, flow was titrated at 2 L/kg/min with a maximal flow of 10 L/min. In infants with a high RR, relatively high-flow rates are needed to match the maximal inspiratory flow of the patient. The choice of 2 L/kg/min is based on the fact that in the past with the older generation of continuous-bias-flow ventilators, the bias flow was set at 2 L/kg/min to match the high inspiratory flows.

Another finding was that we were able to wean the HFNC to room air (21% O2) before the HFNC was switched off, and no weaning of the flow rate was allowed. The oxygen in the control group was weaned from 2 L/min to off according to SpO2. This approach followed a shift in paradigm that considers that an early oxygen requirement can be treated with CPAP by recruiting previously collapsed lung regions. The weaning approach did not prolong the time of respiratory support or hospital LOS.
Limitations
This study may be criticised because of its non-randomised design. Our ethics review board denied us permission to perform a RCT and requested a pilot study investigating the safety of HFNC treatment first. After completion of the study, we were allowed to retrospectively analyse a case control group (standard oxygen therapy) of all infants with bronchiolitis who were admitted within the same time frame and fulfilled the inclusion criteria but were not enrolled in the study (due to the study investigator not being contacted). This group matched the study group in their demographic and physiological data on admission and were treated in the same paediatric ward using the same 1:4 nursing ratio and hospital bronchiolitis management protocol. The small number of patients in the study does not allow for a strong conclusion, and only a RCT will address the question of the effects of HFNC treatment in the ward environment.

Conclusion
This pilot study produced interesting results on the safety of HFNC treatment in a ward environment. It gives guidelines as to how a larger RCT may be conducted. Physiological parameters such as HR and RR correlate well with the response to treatment and hence potential PICU admission. With viral bronchiolitis being the most common reason for non-elective admissions to PICUs in Australia, using HFNC treatment in paediatric wards may result in substantial cost savings without impact on safety of patient care. It would be worthwhile to undertake a RCT and investigate the fiscal implications of reducing PICU admissions by utilising this treatment in the ward environment.

Acknowledgements
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References
Chapter 7: Discussion

7.1 Introduction
The preceding chapters have presented the current literature and evidence for the management of bronchiolitis, including with HFNC, and the methodology and results of the pilot study. This chapter will discuss the findings from the case series, systematic review and pilot study, and expand on the strengths and limitations of the thesis.

7.2 Case series
The purpose of the case series was to describe three typical cases of patients admitted to the PICU, and the use of HFNC therapy. The pathophysiologies chosen were representative of causing moderate to severe respiratory distress, either in the upper airways (asthma), lower airways (bronchiolitis) or due to cardiac disease (cardiomyopathy). Before this, the use of HFNC as a treatment in paediatric patients for respiratory compromise from varied pathophysiologies had not been reported. In each presented case, HFNC therapy was used successfully and there were no adverse events, such as air leak syndrome, nasal trauma or abdominal overdistention. However, these results cannot be externally generalised due to inherent limitations with case series methodology.

7.2.1 Limitations of case series
Case studies can be a valuable research and educational resource and when reported around a particular aspect of care – they can provide new insights and stimulate research in response to knowledge gaps. In areas of rapid clinical change, case series can present and discuss new therapies in a timely manner. However, they have limited external validity, and are low on the hierarchy of level of evidence.\textsuperscript{163,186}

7.2.1.1 Potential bias
The cases were selected because they were typical presentations of PICU patients with the intention to find and describe the common progress of patients being managed with HFNC therapy in PICU. However it is conceivable that each case was unwittingly chosen because there was a positive clinical course using HFNC therapy.

Data entry was another source of potential bias. The data was extracted from the PICU clinical information system, however it was manually entered into Microsoft\textregistered Excel 2010
worksheets. Human factors may influence the accuracy of the data entry. However, in an attempt to mitigate this and provide data integrity, validation strategies were implemented within the worksheets, and data was manually and visually inspected by an independent person.

### 7.2.2 Summary of case series

The case series suggests that HFNC therapy may be an effective treatment for patients with respiratory distress due to underlying pathophysiologies of asthma, bronchiolitis and cardiomyopathy. Using HFNC therapy may prevent invasive ventilation in these three clinical scenarios, improve recovery times, and shorten length of PICU stay. However, there is limited generalisability to populations as a whole due to the inherent weakness of case series.

While these patients were admitted to the PICU, it is possible that the infant with bronchiolitis could have been managed on a ward, if there was a hospital protocol and policy in place to support this. In order to address the possibility of administering HFNC therapy on a paediatric ward, a systematic review of the evidence and pilot study were undertaken.

### 7.3 Systematic review

The purpose of the systematic review was to identify and synthesise paediatric studies on the use of HFNC. By pooling data from homogenous studies into a meta-analysis, statistical significance may be found supporting either a positive or negative impact of HFNC. This can further inform clinical practice.

As The Cochrane Collaboration is the gold standard for conducting systematic reviews, the reviews were undertaken with this organisation. Due to the age of infants (from birth up to 44 weeks post-term), two reviews were required with two different Cochrane groups.

#### 7.3.1 Limitations of systematic review

The Cochrane Neonatal Review Group (CNRG) administers all reviews on pre-term infants, including those post term up to 44 weeks while the CARG excludes this cohort from their reviews. Infants aged term to 44 weeks post gestational age (or 28 days old) are one of the most frequently admitted sub-groups to Australian PICUs, comprising 9% of total admissions (and a quarter of those <12 months old). This pattern is likely mirrored internationally. Therefore, to fully address the use of HFNC within paediatric populations, it
was essential that the full age spectrum of children was explored; hence, two protocols were conducted with different groups.

While this allowed the exploration of discrete data around neonates versus children, it constrained the ability to present all data from one source, that is, the CARG review. It is perhaps important to have less rigidity around the grouping in this age group – most reviews with the CNRG centre on pre-term infants (those <37 weeks gestation and cared for in a NICU). For those infants >37 weeks gestation and up to 44 weeks, who are included in paediatric studies because they are admitted to a paediatric facility, there should be the provision to include them in the one systematic review. Of note, the Acute Respiratory Review Group do not place any limitations on the overlap of age with the CNRG, as evidenced by the review into HFNC and bronchiolitis with a stated age of less than 24 months.\textsuperscript{144}

7.3.2 Summary of systematic review

While the systematic review completed with CARG was an important exercise, the lack of identified studies that met the inclusion criteria meant there was nothing to report. However, some identified upcoming clinical trials may meet the inclusion criteria and be able to be included into the two-yearly reviews.

7.4 Pilot study

The purpose of the pilot study was to investigate the use of HFNC therapy to manage infants with bronchiolitis in the paediatric ward. Bronchiolitis was isolated as a pathophysiology, over asthma and cardiomyopathy detailed in the case series, due to the prevalence of this condition and the potential impact on practice change. Choosing infants with bronchiolitis allowed maximum homogeneity within the sample.

7.4.1 Key results

The aim of the pilot study was to assess the safe and efficient use of HFNC therapy outside of the PICU. The primary outcome to support the aim was admission to PICU. The pilot study showed that HFNC therapy for infants with bronchiolitis, commenced early in the PED, reduced admission to the PICU. Moreover, the study demonstrated that effective response to the therapy could be determined at 60 minutes post-application by assessing physiological variables such as heart rate and respiratory rate, and considering a composite score of all variable (as determined within early warning tools). Previous
studies have identified a reduction in heart rate as a measure of clinical improvement in paediatric populations following HFNC therapy.\textsuperscript{15,147} This concurs with other studies describing a similar response-to-treatment time observations.\textsuperscript{15,145–147,149} The significance of this is that infants who may ‘fail’ treatment can be identified early in their course, with an appropriate response of PICU review and/or admission, thereby adding a level of safety and quality to the management of these infants outside of high acuity areas.

No major adverse events (cardiac arrest, air leak syndrome, bradycardia) occurred in the pilot study, and few to none are reported in recent paediatric publications.\textsuperscript{15,143,146–149,151,152} However, it remains an important and valid concern. While air leak syndrome has been reported in a case series by Hedge and Prodhan,\textsuperscript{154} no substantive link conclusively determined if HFNC therapy was the cause of the air leak events. Indeed chance, selection and reporting biases inherent in case series methodology could account for these adverse events. Yet it remains a reasonable concern, and being aware may increase clinician vigilance surrounding these potential and specific adverse events in implementing HFNC therapy for any patient.

Further, of the pilot study infants receiving HFNC therapy who were admitted to the PICU (8%), none required intubation. This result again is reflected in the small number of paediatric studies that have investigated HFNC use in the ward environment.\textsuperscript{143,149}

7.4.1.1 Key post-hoc results

Although not a primary or secondary outcome identified in the design of the pilot study, there has been burgeoning interest in how infants receive their nutritional support while on HFNC. A number of paediatric studies have reported that oral feeding has been tolerated in this group.\textsuperscript{143,145,146,149,150} Oral feeding is a clinically important variable and one that justified post-hoc analysis. In the pilot study, 35% of infants on HFNC were orally (either bottle or breast) fed, with a further 31% receiving a combination of oral and nasogastric feeding during the study period. None of those orally fed were admitted to PICU. In the ward in which this study was conducted, nurses are the front-line staff that monitor, assess, identify and implement changes to feeding protocol. Therefore, this result suggests that those infants responding to HFNC therapy, as identified at 60 minutes, are likely to be able to orally feed, and that nurses at the bedside are able to distinguish between those who can manage oral feeding and those who cannot.
7.4.2 Limitations to the pilot study

Pilot studies have numerous purposes and are an important way to explore feasibility,\textsuperscript{182} with lessons learned preventing major problems in the planning and running of a larger study. With this pilot study into the use of HFNC in the paediatric ward, some limitations require further elaboration and exploration.

7.4.2.1 Institutional constraints with study design

Within the realm of evidenced based health care, the hierarchy for assessing the degree to which information from research can be trusted are termed ‘levels of evidence’.\textsuperscript{163} Traditionally, levels of evidence are presented in a pyramid format (described in Chapter 4), with meta-analysis and systematic reviews at the pinnacle, closely followed by well-constructed RCTs. When designing the HFNC study, the initial plan was conduct it as an RCT, the gold standard for assessing a specific therapeutic intervention. However, in June 2010, conversations with the Executive Director of the Mater Children’s Hospital and the Hospital Board made it clear that a request to conduct an RCT in the ward environment would be refused. While it is not possible to reconstruct the processes and rationale which led to this decision, it is likely that the absence at that time of any precedent studies centred in a paediatric ward, and concerns over the safety of using this therapy outside of the ICU held considerable influence. Consequently, by way of compromise, a pilot study design was proposed and subsequently received institutional approval. One concession of the revised study design is the claim to external validity for the findings – the extent to which they can be generalised to other situations may be limited.

The study initially envisaged that children aged 1 day to 24 months with a diagnosis of bronchiolitis, and admitted to two specific paediatric wards (one public and one private) at the Mater Children’s Hospital, would be considered for inclusion in the study. However, access to one of the wards was denied by the then Acting Director of Nursing (A/DON), on the basis that it would too difficult for the private ward to be involved in a study. This gatekeeping limited the study to one public ward which only admitted infants aged 1 day to 12 months and resulted in systemic restrictions to the inclusion criteria. Not only was the age restricted to 1 day to 12 months, but before consent, parents needed to be screened as to their private health fund status. Parents who chose to be admitted to the private ward were not approached for participation in the study. However, some parents chose not to use the option of having their child admitted as a private patient, consented to the study and were admitted to the public ward. No other changes occurred in the way the patients were managed except for using HFNC therapy.
Potential bias was introduced into the study by the selection of participants. While criteria for inclusion and exclusion existed, and all staff had been extensively educated on the study protocol, it became apparent that many potential study participants were being missed. This was determined from the meticulous screening log that was kept during the recruitment period and that was retrospectively updated during the week from the PED database (EDIS™), which is managed 24/7 by the PED ward clerks. Every patient who is triaged is entered into the database with their demographic details and initial diagnosis, ensuring the database is a reliable source of data of patients seen in the PED.

The use of PED medical staff to consent patients to the study proved to be an institutional constraint, as recruitment and consent of patients was perceived by the PED Director as additional work for PED doctors. Changes were therefore made, and the author carried out recruitment, with availability 24/7 for the duration of the study recruitment period. Initially nursing staff were hesitant to call late at night and in the early morning, but as the study progressed, staff became more engaged and called at all hours when a patient was identified. This may have introduced some potential for systematic bias in recruitment in the early stages of the study. However, analysis of the demographic, physiological, clinical and treatment characteristics of the intervention and comparison groups demonstrated that there was no difference between the groups.

Calculation of the sample size was a limitation, and Chapter 5 acknowledged the difficulty of sample size calculation for pilot studies. Briefly, these include cost, realistic timeframes, and intention and outcomes desired for the planning of the larger RCT. The result was that the method for calculating a true sample size of effect was not ideal. However, as this was a pilot, and there was an assumption of a decrease in PICU admissions, the sample size was sufficient to enable power calculations for the RCT.

Another potential limitation was that the nursing staff could not be blinded to the study group. It is reasonable to suggest that this could lead to observation bias of staff in their documentation, even with a protocol in place. This raised the possibility of nursing staff unconsciously influencing the outcome, especially in relation to the timing of referral or non-referral to the PICU. This could affect internal validity of the study results. A plan to mitigate this was implemented in the form of conscientiously following up the patients, to determine nursing staff understanding, adherence, and satisfaction with the protocol. Staff education during the study period was continued by the Nurse Educator contracted to the study.
Even with conscientious follow up of the study patients, a number of protocol violations occurred, involving paediatric consultant medical staff. These were spread evenly over the study period, with four recorded in the first 30 patients and 4 in the second 31 patients. The violations consisted of consultants increasing the FiO₂ in response to increased work of breathing, despite the patient saturating at >98% via peripheral plethysmography. This resulted in patients not being weaned from oxygen as per the protocol, a violation that could potentially lead to an increased length of therapy time. To remedy this, a PICU intensivist reiterated the study protocol to the consultants. On the whole, the majority of consultants did have 'buy-in' to the study, and realised that there were safety procedures in place to identify the deteriorating patient, and that admission to PICU would not be compromised.

Nurses were also responsible for protocol violations in not weaning the FiO₂ when saturations (SaO₂ via peripheral plethysmography) was >98%. In one case, the patient was left on a FiO₂ of 0.3 with SaO₂ recorded at 99% for 20 hours. While this did not cause any harm to the patient, it is reasonable to conclude this may have extended the patient's stay in hospital. This incident highlighted the inherent weakness in any clinical study relying on clinicians to consistently adhere to study protocols.

7.4.2.3 Early warning tools

While the use of an early warning tool was justified in Chapter 5, there remain limitations behind the particular use of the CEWT and its modification into the HiFOD collection form.

Early warning tools are designed to assist clinical staff in recognising the deteriorating patient, reducing response delay and thereby preventing avoidable mortality and morbidity. Within paediatrics exist a number of either validated, peer reviewed, and/or published early warning tools, such as the Brighton Paediatric Early Warning Score, the Bristol Paediatric Early Warning Tool (PEWT) and a number of others that have been modified to suit specific cases. CEWT closely resembles the Bedside PEWSS and was initially tested on infants with bronchiolitis. However, it has not been prospectively validated, peer reviewed nor published.

Using any of the tools named above would have been appropriate to capture physiological data during the study, and to provide an extra level of 'safety' as they have been prospectively validated and are considered reliable (Table 7.1). The sensitivity (that is, measures of the proportion of actual positives) and specificity (that is, actual negatives that
are correctly identified as such) of each tool are important in determining their ability to correctly identify those patients who are deteriorating. ROC curves of greater than 0.80 are considered to be significant and support assumptions of tool validity and the ability to predict actual deterioration. The Brighton PEWS and the Bedside PEWSS satisfy this in the prospectively validated studies.

However, as the Mater Children's Hospital was to imminently roll out the CEWT (Appendix 3), which had been approved and incorporated into Queensland Health hospitals, institutional constraints demanded the use of the CEWT tool over any other. For this study, one modification to CEWT was required to capture the flow rate and FiO₂ of the equipment, hence the name change to HiFOD. It was not until the final 4 months of the pilot study that the CEWT was rolled out in the study ward for all patients.

A consequence of using an unpublished and unvalidated tool (CEWT in the form of HiFOD) for the pilot study was that the composite scores were not reported in the published paper. The manuscript peer reviewers and the journal editors recommended that in the absence of published evidence of the CEWT validity and reliability, data composite scores be excluded from the manuscript. Yet, a recent review of paediatric early warning systems incorporated into hospitals in the United Kingdom found that the majority of systems implemented in hospital institutions were unpublished and unvalidated.

After 2010, the development and use of early warning tools has greatly expanded in Australia. New South Wales, Victoria and Australian Capital Territory all have paediatric early warning system tools in place, which have many similarities with CEWT, but minor differences in weighting of scores and what triggers a medical emergency team call.

7.4.2.3.1 Sensitivity and specificity
For the purpose of attempting to validate the HiFOD score for patients requiring HFNC, area under the curve ROC analysis was undertaken. The inclusive HiFOD score had a ROC curve of 0.80 from 61 participants. However, with the comparison group comprising only 33 patients, the numbers were too small to provide a clear indication of the true sensitivity and specificity of the HiFOD tool to accurately predict the deteriorating patient. At best, the ROC curve may describe a positive predictive value of the HiFOD score. This idea was elaborated on in a response article to the Bristol PEWT, which questioned this tool's true ability to claim sensitivity and specificity. Further analysis on the performance of the HiFOD and CEWT tools is essential, as is that true and valid sensitivity and specificity is determined at specific values, such as has been done with the Bedside
PEWSS. However, it is beyond the scope of this thesis to provide further analysis and validation of the CEWT/HiFOD tool, or of other "track and trigger" systems in use in Australia.

Table 7.1 – Comparison of paediatric early warning tools validation

<table>
<thead>
<tr>
<th>Components</th>
<th>Brighton PEWS\textsuperscript{181,187}</th>
<th>Bedside PEWSS\textsuperscript{188,193}</th>
<th>Bristol Paediatric Early Warning Tool (PEWT)\textsuperscript{180}</th>
<th>HiFOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>3 items, score range 0–9</td>
<td>7 items, referenced to age, score range 0–26</td>
<td>5 items (A to E) with sub items (2–4)</td>
<td>9 items referenced to age, score range 0–12</td>
</tr>
<tr>
<td>Initial study – participants</td>
<td>unknown number over 3 months</td>
<td>87 cases, 128 control, single centre</td>
<td>360 patients over 6 months</td>
<td>61 patients over 10 months</td>
</tr>
<tr>
<td>Initial study – sensitivity and specificity (%) respectively</td>
<td>Not reported</td>
<td>0.78 and 0.95 at score 5</td>
<td>0.66 and 0.99 to trigger the tool</td>
<td>0.80 and 0.40 at score 5</td>
</tr>
<tr>
<td>Initial study – ROC</td>
<td>Not reported</td>
<td>0.90 in initial study, 0.87 in prospective study</td>
<td>Not reported</td>
<td>0.80</td>
</tr>
<tr>
<td>Prospectively validated study</td>
<td>2979 patients, newborn to 22 years, over 12 months, single centre</td>
<td>2074 patients, international, multicentre case control (4 hospitals)</td>
<td>Not prospectively validated</td>
<td>N/A</td>
</tr>
<tr>
<td>Sensitivity and specificity (%) respectively</td>
<td>0.33 and 0.99 at score 7; 0.13 and 0.99 at score 8</td>
<td>0.64 and 0.91 at score 7; 0.57 and 0.94 at score 8</td>
<td>Unknown</td>
<td>N/A</td>
</tr>
<tr>
<td>ROC</td>
<td>0.89</td>
<td>0.87</td>
<td>Unknown</td>
<td>N/A</td>
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ROC = Receiver operator characteristic

7.4.3 Outcomes of pilot study

A secondary aim of the pilot study was to inform the sample size for a larger, multi-centre RCT. Currently (as of mid-2014), a larger study with a target of 800 participants has commenced in regional centres in South East Queensland. Another outcome of the pilot study has been the implementation of HFNC therapy into the routine management of infants with bronchiolitis on the study ward. When the results of this pilot study were presented to the Executive Board of the Mater Children's Hospital, this treatment protocol
and therapy received their endorsement. The pilot study has informed the development of clinical guidelines (Appendix 7) that now govern clinical practice in using HFNC in the study ward.

### 7.4.4 Summary of pilot study

The pilot study has demonstrated that HFNC can be used within a paediatric ward setting. Patients who may not respond to HFNC therapy can be identified within 60 minutes. The likelihood of adverse events associated with HFNC therapy is low. While HFNC therapy may not alter hospital length of stay, it may reduce admission to PICU. Infants can be orally fed while on HFNC therapy, but this requires expert clinical judgement. This remains a small sample of patients and the ability to generalise to a wider population is still restricted. To conduct a larger, multi-centre RCT, approximately 800 participants would be required to achieve the null hypothesis.

### 7.5 Conclusion

While the institutional constraints originating from the Mater Children's Hospital have been addressed and overcome, for other institutions it opposition to HFNC therapy may still remain. Objections revolve around the themes such as:

- **Safety** –
  - Does HFNC therapy mask symptoms of the deteriorating child?
  - Are these infants and children at risk of delayed specialist care due to being managed in a ward?

- **Quality** –
  - What is the true financial benefit of reduced PICU admissions?
  - Is there a measurable psychosocial impact on parents, families and communities?

- **Perception** –
  - What are the underpinning feelings and thoughts of clinicians when considering the implementation of a new therapy?

For these to be overcome and addressed at an institutional level, rigorous discussion is needed involving all key stakeholders, in an environment that is open and safe. This discussion needs to not only consider expert opinion, but understand the value research adds to the decision-making process. Ultimately what is needed in paediatrics is a large-
scale RCT that can answer many of the safety issues that have been speculated in retrospective and observational studies with HFNC therapy.

This chapter has discussed the key results of this thesis, exploring the limitations of the case series, systematic review and the pilot study. The final chapter will detail recommendations for further consideration and conclude the overall evidence for HFNC therapy.
Chapter 8: Recommendations and conclusion

8.1 Introduction
The previous chapter discussed the results and limitations of the case series, systematic review and pilot study undertaken for this thesis. This chapter will present recommendations for further study, and conclude the results in the context of current evidence and theory.

8.2 Summary
This thesis aimed to acquire and disseminate knowledge through research that would guide clinicians using HFNC therapy for managing infants with respiratory distress. Evidence for the use of HFNC has been developed at the level of case series and pilot study, with ongoing two-yearly evaluation of two systematic reviews. These reflect the use of HFNC within both high acuity areas, such as PICUs and low acuity areas, such as paediatric wards. Both the case series and pilot study have added to the growth of literature in the paediatric forum for HFNC use.

Dissemination of knowledge to guide clinicians has been achieved through publications, which describe the use of HFNC in a case series, present systematic review using The Cochrane Collaboration framework, and the completed pilot study. These publications, generated from this thesis, appear in relevant, peer-reviewed journals, ensuring the wide distribution of the findings. The impact factors of the journals are: 1.193 – Journal of Paediatric and Child Health; 1.265 – Australian Critical Care; and 5.939 – Cochrane Collaboration of Systematic Reviews. The pilot study has been presented at local, national and international conferences, further ensuring dissemination across a wide range of paediatric clinicians and researchers.

8.3 Recommendations
This thesis has shown that HFNC therapy in the ward may reduce admissions to PICU. Those not responding to therapy, 'non-responders', may be identified within 60 minutes. There need not be any changes to existing nurse to patient ratios, and nutritional delivery options are described. Yet other potential outcomes and benefits exist that are beyond the scope of the thesis. Further work could be done in the areas of staff experience, patient/parent satisfaction, financial benefit, mode of feeding, and clinical use.
8.3.1 Staff experience
Clinician acceptance of a clinical therapy or practice is key to the successful uptake of change.\textsuperscript{194} While the pilot study did not formally examine the experience of staff in using HFNC in the ward setting, there was anecdotal support for the therapy from the ward Nurse Unit Manager, Nurse Educator and clinical staff using HFNC. Other studies have briefly mentioned preferences for HFNC, such as mentioned by Hilliard et al.\textsuperscript{143} A factor to Hilliard's study concluding early was the bias staff had towards using HFNC therapy instead of traditional head box for infants with bronchiolitis. The HFNC equipment was easy to use and allowed for easier nursing care.\textsuperscript{143} This theme was also present as a component of a thesis by Peeler.\textsuperscript{195} However studies examining in detail staff experience in using HFNC are absent, and this may be worthy of further investigation.

8.3.2 Patient/parent experience
Understanding the perceptions of patients and parents when introducing a change in therapy or practice can be powerful in developing cohesion between health professionals and patients/carers. While the pilot study did not include a formal interview or questionnaire, the opinion of parents was sought during the daily ward rounding. Anecdotally, parents often stated that they could see the positive effect that HFNC was having on the breathing of their infant. They found HFNC allowed them to hold their infant and on occasion breast feed, which allowed the mother a sense of connectedness. This has been explored in detail in the thesis by Peeler,\textsuperscript{195} however within paediatric literature there are no publications surrounding the patient or parent experience with HFNC use. While comfort levels are reported within adult studies\textsuperscript{128,130,132} and the COMFORT score has been reported as a surrogate measure for tolerance of HFNC itself,\textsuperscript{80} no published studies illuminate this important aspect of HFNC therapy. Examining this would be of benefit, but beyond the scope of this thesis.

8.3.3 Cost–benefit
An impediment to the successful uptake of clinical practice change can be perceptions of practical benefits gained versus financial cost.\textsuperscript{196} While Martinez\textsuperscript{150} stated that there was a significant cost saving in managing infants within the ward using HFNC therapy as opposed to the PICU, there was no robust detail that quantified the financial gain, which limited the ability to independently assess the claim. It would be appropriate to assess and quantify the health economics of implementing HFNC use in paediatric wards. While cost saving should never replace safety concerns, nor be a factor in managing children in lower
acuity areas, it remains a relevant and important area for further investigations. These questions are, however, beyond the scope of this thesis.

8.3.4 Mode of feeding
The optimal method of feeding while receiving HFNC therapy is an unknown quantity. Within the pilot study, the mode of feeding was discerned from post-hoc analysis, and was not an intended outcome. While there is growing consideration of this aspect of treatment in recent neonatal and paediatric literature, to date no published controlled trial or observational study has focused on describing or managing infant and child nutrition while on HFNC therapy. To address this gap in knowledge, a study is being undertaken on the pilot study ward at Mater Children’s Hospital, following the implementation of clinical practice guidelines.

8.3.5 Clinical use
Practice use of HFNC therapy in neonatal nurseries has been explored in both Australia, New Zealand, and the United Kingdom. The surveys have found that use of HFNC is widespread and clinical practice is diverse. Anecdotal evidence obtained from conversations with many clinicians at international and national conferences has revealed increasing uptake of HFNC use in paediatric wards. This practice creep is unknown in terms of when, how, and who guides and implements this treatment option. A detailed survey of paediatric hospitals (and wards within adult hospitals) within Australia and New Zealand on their use of HFNC may be worthy of further investigation.

8.4 Conclusion
Overall this thesis has demonstrated that HFNC therapy is a useful adjunct in managing infants and children with respiratory distress. The case series underpinned the use of HFNC therapy across a wide spectrum of pathophysilogies, and the positive course that may follow. It further adds to the body of evidence for HFNC therapy use in the PICU, and expands its use from just infants with bronchiolitis. The pilot study further showed that implementing HFNC therapy in the paediatric ward environment may reduce admissions to the PICU. The pilot study also established that physiological parameters can alert a clinician to the early response of a patient to the therapy. If there is no meaningful decrease in heart rate, respiratory rate or composite score within 60 minutes of therapy initiation, there is a high probability that the patient will require specialist care and observation in an ICU.
There is no doubt that practice creep in using HFNC therapy is growing throughout the world, and in all hospital settings. Yet no large RCT has produced evidence that completely underpins and validates HFNC therapy. This is true for paediatrics, neonates and adults. However, the pilot study from this thesis has been instrumental in advising a large, multicentre RCT currently under way in South East Queensland, Australia.

Ultimately, this thesis has achieved its aim and contributed significantly to understanding the use of HFNC therapy for children and infants with respiratory distress. The Cochrane Collaboration review, case series, and pilot study have all contributed to the total body of knowledge surrounding HFNC therapy in the paediatric population. This will improve outcomes by assisting clinicians in their decision-making process for implementing and assessing appropriate treatment options, and aid in guiding researches in further exploration of this subject.
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<td>DECLARATIONS OF INTEREST</td>
<td>26</td>
</tr>
</tbody>
</table>
**ABSTRACT**

This is the protocol for a review and there is no abstract. The objectives are as follows:

We aim to determine if the use of HFNC is better than other forms of non-invasive therapy in paediatric patients who require respiratory support.
BACKGROUND

Description of the condition
Respiratory support is central to the care of critically ill children. Support may be needed due to underlying disease processes such as respiratory infections or pneumonia, neuromuscular disorders, cardiac conditions or failure, and other mechanisms such as upper airway obstruction, trauma and injury, or post-surgical interventions. Respiratory support can be delivered non-invasively in the form of oxygen therapy or continuous positive airway pressure (CPAP) or invasively via mechanical ventilation. Children with significant respiratory distress and hypoxaemia often require the latter. This may result in various forms of trauma to the lungs and airways, collectively known as ventilator induced lung injury (VILI) (Dahlem 2003; The ARDS Network 2000).

While VILI is the major concern with intubation and mechanical ventilation, there are other effects on the body that need to be considered. The increased use of sedative drugs may lead to neuropathy or myopathy, which can increase recovery time. In turn there may be the need for cardiovascular support in the form of drug infusions to maintain blood pressure. All of these factors increase the costs of the care provided to the child. Non-invasive methods of ventilation are an ideal method of providing respiratory support without the need for intubation and may avoid some of the additional harm associated with positive pressure ventilation. Non-invasive ventilation can be as simple as oxygen therapy delivered via a face mask, nasal cannula or head box through to devices delivering CPAP via the face and mask interface or nasopharyngeal tubes, with pressure generated by a dedicated driver or water column (that is bubble CPAP) (Frey 2001; Frey 2003; Klein 1986).

Those devices delivering CPAP can reduce the work of breathing and improve functional residual capacity, potentially avoiding intubation, reducing VILI, and preventing other possible causes of harm (Reid 1984; Thorsteinsson 2002). A disadvantage of this method of delivery is that it is cumbersome and the masks and tubes used are poorly tolerated by young children and infants (Yong 2005). This can make the delivery of CPAP variable thereby resulting in ineffective ventilation. Having a system that can deliver CPAP and be comfortable and well tolerated by children is an important consideration in providing non-invasive respiratory support.

Description of the intervention
High flow nasal cannula (HFNC) therapy has recently been introduced to a range of patients from preterm infants to adults, addressing the need for a simple, effective method of providing respiratory support (Campbell 2006; McGinley 2009; McKiernan 2009; Shoemaker 2007). It has an advantage over simple oxygen therapy in that the gas mixture can be heated and humidified, thereby reducing damage to upper airway mucosa, and the concentration of inspired oxygen can also be titrated as required. This can prevent inflammatory reactions and the naso-pulmonary bronchoconstrictor reflex triggered by cold, dry air (Spentzas 2009).

It has been shown that the delivery of nasal air at high flow rates may cause incidental delivery of CPAP (Dysart 2009; Spence 2007; Wilkinson 2008). The effects of this are yet to be fully understood. It may be that the high flow flushes the dead space of the nasopharyngeal cavity resulting in alveolar ventilation as a greater fraction of minute ventilation. It may also assist in the washout of carbon dioxide, which may then reduce apnoeas secondary to hypercapnia and improve ventilation (Dysart 2009). High flow rates may also provide an amount of positive pressure and thereby overcome upper airway obstruction, again improving ventilation (McGinley 2009).

The amount of CPAP generated depends on the flow delivered relative to the size of the patient, the size of the nasal cannula used, and the potential leak around the nasal cannula (Kubicka 2008; Lampland 2009; Sreenan 2001). Three retrospective studies assessing HFNC therapy have demonstrated that overall ventilator days were significantly decreased after the introduction of this therapy when compared to retrospective historical control groups (McKiernan 2009; Schibler 2011; Shoemaker 2007). HFNC therapy has also been reported to be better tolerated by the patient than other forms of non-invasive ventilation (Roca 2010). This can reduce the need for sedation that is required to help tolerate more invasive or uncomfortable forms of respiratory support.

Why it is important to do this review
HFNC therapy is an emerging treatment option for the respiratory support of children, especially in the intensive care unit. To date, most of the findings have been from neonatal and adult studies, with little clinical experience reported in the paediatric population (McKiernan 2009). The Cochrane review on high flow nasal cannula from the Cochrane Neonatal Group concluded that there is insufficient evidence to determine HFNC effectiveness and that more research is needed (Wilkinson 2011). At present there is a protocol for the systematic review assessing HFNC effectiveness in the adult population, which is in progress with the Cochrane Anaesthesia Group (Corley in process). There is also a protocol with the Cochrane Acute Respiratory Infections Group assessing HFNC therapy for infants with bronchiolitis (Beggs 2012). This review differs in that it covers a wider age range and more diverse pathophysiologies.

It is necessary to assess the use of this therapy amongst the paediatric population as there are potential risks associated with its use. Neonatal studies have described scalp emphysema and pneumocephalus as potential risks, along with nasal mucosal trauma and bleeding (Jasin 2008; Kopelman 2003). There is also concern that this therapy in the neonatal population provides unpredictable,
high pressures that could damage the preterm lung (Lampland 2009). These risks need to be assessed in the paediatric population.

HFNC has the potential to improve outcomes in critically ill children. It is readily applied and is not resource or cost intensive. Staff can easily be trained in the application of HFNC and in the care of children using this therapy. It may reduce the incidence of intubation in paediatrics and may reduce the length of intubation as HFNC holds potential as an adjunct between extubation and low flow nasal prong oxygen delivery. The potential also exists that children requiring this therapy may be cared for outside of the paediatric intensive care unit (PICU).

OBJECTIVES

We aim to determine if the use of HFNC is better than other forms of non-invasive therapy in paediatric patients who require respiratory support.

METHODS

Criteria for considering studies for this review

Types of studies
We will include prospective, randomized controlled trials (RCTs) and quasi-randomized studies.

Types of participants
We will include paediatric participants aged from four weeks corrected age to 16 years requiring respiratory support.

Types of interventions
For the purposes of this review, we will define high flow nasal oxygen as the delivery of heated, humidified oxygen or blended oxygen with air via a nasal cannula at flow rates of greater than 2 L/minute. HFNC will be compared with other means of non-invasive respiratory support, such as cot, hood or tent oxygen; low flow nasal cannula (flow rates equal to or less than 2 L/min); and continuous positive airway pressure (CPAP).

Types of outcome measures

Primary outcomes
1. Hospital mortality

Secondary outcomes
1. Duration of any form of respiratory support in hours (mechanical ventilation, non-invasive ventilation, high flow nasal cannula)
2. Length of stay in days in hospital
3. Clinical severity score
4. Length of PICU stay in days
5. Complications:
   • air leaks (pneumothorax, pneumomediastinum, pneumopericardium or pulmonary interstitial emphysema (PIE)) reported either individually or as a composite outcome
   • nasal trauma (defined as erythema or erosion of the nasal mucosa, nares or septum assessed by a blinded observer)
   • nosocomial sepsis (defined as positive blood or cerebrospinal fluid (CSF) cultures)
   • barotrauma
   • gastrointestinal distention

Additional outcomes measured in trials will be added as secondary outcomes following the literature search.

Search methods for identification of studies

Electronic searches
We will obtain all relevant studies irrespective of language or publication status (published, unpublished, in press, and in progress) using the following methods. We will apply no limits in terms of language or year of publication.

We will search the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library); MEDLINE via Ovid SP (January 1966 to date); EMBASE via Ovid SP (January 1980 to date); CINAHL via EBSCO Host (1982 to date); LILACS via the BIREME interface (1982 to date).

We will search electronic databases of higher degree theses for relevant unpublished trials: Index to Theses (1950 to date), Australian Digital Theses Program (1997 to date) and Proquest Digital Dissertations (1980 to date). We will search the Meta Register of Controlled Trials (http://www.controlledtrials.com/) and the National Research Register (http://clinicaltrials.gov/).
Searching other resources

We will handsearch citations from included studies. We will not exclude studies on the basis of language. We will contact authors known in the field to determine if unpublished work is available.

Data collection and analysis

Selection of studies

Six authors (SM, JJC, FB, JH, AS, KG) will undertake the review. We will use the search strategy described to obtain titles and abstracts of studies that may be relevant to the review. Two authors (SM and JJC) will independently perform this screening. We will discard studies that are not applicable, and the reason for each trial that is excluded will be documented. We will resolve disagreements by consulting with a third author (FB), who will decide on inclusion or not.

We will compile a list of eligible trials, with a unique identifier, on a form for eligible trials contained within the data extraction form (see Appendix 2).

Data extraction and management

We will adapt the standardized Cochrane Anaesthesia Review Group (CARG) data extraction form (Appendix 2) to capture relevant data specific to this review. We (SM and JJC) will use this form independently to extract and collect data from the relevant studies. We (SM and JJC) will resolve any discrepancies in the data extracted by discussion.

Assessment of risk of bias in included studies

Two authors (SM and JJC) will independently assess the methodological quality of the eligible trials. Any disagreements will be resolved by a third author (FB). We will include a risk of bias table as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The judgements ‘low risk’, ‘high risk’ and ‘unclear risk’ will be used in the table to determine bias. SM will enter the data into the Review manager Software (RevMan 5.1) with verification of data entry conducted independently. The following domains will be assessed.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel, and outcome assessors.
4. Intention-to-treat analysis.

We will use pre-defined criteria for treatment failure (switching to an alternative respiratory support modality) and intubation.

Measures of treatment effect

We will summarize trials that meet the inclusion criteria in tables to allow for comparison of characteristics and quality. Excluded studies will be tabulated with the reason for exclusion documented. For dichotomous outcome data, such as mortality, we will use risk ratio (RR) to determine effect. It will be displayed on a table as ‘number with event’ and ‘number without event’. For continuous data we will collect the mean and standard deviation and display it on a table. If different scales are used to measure continuous data across trials we will calculate the standardized mean difference (SMD) to determine treatment effect.

We will analyse outcomes from comparable trials with 95% confidence intervals (CI) to estimate each trial’s treatment effect. We will compare the results graphically using forest plots, with risk ratio (RR) as the point estimate for dichotomous outcomes and mean difference (MD) as the point estimate for continuous outcomes.

Dealing with missing data

We will contact the corresponding author of the study to source missing data. If the corresponding author does not respond, or if it is not possible to find them, then we will include the trial in question in the review but we will analyse the effects of its inclusion or exclusion on the overall results as part of the sensitivity analysis.

Assessment of heterogeneity

We will analyse heterogeneity using the Chi² test on N-1 degrees of freedom, with an alpha of 0.1 used for statistical significance, and with the I² statistic (Higgins 2011). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity, respectively. We will set an I² threshold of greater than 50% to indicate a substantial variation across trials due to heterogeneity. We will use a fixed-effect model if we find insignificant heterogeneity between trials. We will use a random-effects model if significant heterogeneity exists between trials (Higgins 2011). We will test for homogeneity between trials for each outcome using the Cochran’s Q statistic, with P less than or equal to 0.10.

We will assess the clinical diversity (clinical heterogeneity) and methodological diversity (risk of bias assessment) of the included studies. We will undertake subgroup analysis to examine possible clinical variability when the I² statistic is less than 50% but heterogeneity remains statistically significant.

We will analyse outcome data from trial populations rather than individuals in order to explain possible sources of variability (Higgins 2011).

Assessment of reporting biases

We will assess publication bias or small study effects by preparing a funnel plot. We will test for funnel plot asymmetry if there are greater than 10 studies included in the meta-analysis.
Data synthesis
We will review the summary tables of included trials to identify clinical heterogeneity amongst trials. If there are two or more randomized trials with comparable populations undergoing similar interventions, we will do a meta-analysis with a random-effects model using RevMan 5.1.

Subgroup analysis and investigation of heterogeneity
We will perform subgroup analysis to explore possible sources of heterogeneity (for example participants, interventions). Heterogeneity among participants could be related to age, corrected gestational age and underlying pathophysiological condition. Heterogeneity in treatment could be related to the amount of flow delivered in relation to body weight. We will explore the impact of differing flow rates with a subgroup analysis. We will tabulate and assess adverse effects with descriptive techniques as they are likely to be different for the various subgroups. Where possible, we will calculate the RR with 95% CI for each adverse effect. We will explore the impact of differing flow rates with a subgroup analysis. We will examine differences in populations based on the following.
1. Age (corrected).
2. Pathophysiology, as follows:
   - type 1 respiratory failure;
   - type 2 respiratory failure;
   - parenchymal lung disease;
   - neuromuscular disorders;
   - respiratory drive;
   - airway obstruction;
   - preterm birth.

Sensitivity analysis
We will perform a sensitivity analysis, exploring the causes of heterogeneity and the robustness of results if there is an adequate number of studies. We will perform sensitivity analysis of trials with low-risk of bias versus high-risk of bias. We will compare random-effects model and fixed-effect model estimates for each outcome variable.

Summary of findings
We will use the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes: mortality, intubation, failure of treatment or escalation to non-invasive ventilation, length of PICU stay, length of time on any form of respiratory support, oxygenation and respiratory assessment tools in our review and construct a summary of findings (SoF) table using the GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers, within a study, the risk of bias (methodologic quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias (Guyatt 2008).

ACKNOWLEDGEMENTS
We would like to thank Mathew Zacharis (content editor), Cathal Walsh (Statistical editor), Dominic Wilkinson, Oliver Karam, Mark Davies (peer reviewers) for their help and editorial advice during the preparation of this protocol for the systematic review.

REFERENCES

Additional references

Beggs 2012

Campbell 2006

Corley in process

Dahlem 2003

Dysart 2009

Frey 2001

Frey 2003
why is it important to clinicians. BMJ 2008;336:995–8. [MEDLINE: 18456631]

Higgins 2011

Klein 2008

Kopelman 2003

Kubicka 2008

Lampland 2009

McGinley 2009

McKierman 2009

Reid 1984

RevMan 5.1

Roca 2010

Schiebler 2011

Shoemaker 2007

Spence 2007

Spentzas 2009

Sreenan 2001

Sutton 2008

The ARDS Network 2000

Thorsteinsson 2002

Wilkinson 2008

Wilkinson 2011

Yong 2005
APPENDICES

Appendix 1. Search strategy for MEDLINE (Ovid SP)

1. (exp Oxygen Inhalation Therapy/ and intubation rates*.af.) or (high flow adj3 (nasal or prong or cannula)).mp. or (nasal adj3 oxygen).mp.
2. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
3. 1 and 2

Appendix 2. Data extraction form

<table>
<thead>
<tr>
<th>Review title or ID</th>
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</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Study ID (surname of first author and year first full report of study was published e.g. Smith 2001)</th>
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<table>
<thead>
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<th>Report IDs of other reports of this study (e.g. duplicate publications, follow-up studies)</th>
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# General Information

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<tr>
<td>Name/ID of person extracting data</td>
</tr>
<tr>
<td>Report title (title of paper/abstract/report that data are extracted from)</td>
</tr>
<tr>
<td>Report ID (ID for this paper/abstract/report)</td>
</tr>
<tr>
<td>Reference details</td>
</tr>
<tr>
<td>Report author contact details</td>
</tr>
<tr>
<td>Publication type (e.g. full report, abstract, letter)</td>
</tr>
<tr>
<td>Study funding sources (including role of funders)</td>
</tr>
<tr>
<td>Possible conflicts of interest (for study authors)</td>
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## Study Eligibility
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<th>Study Characteristics</th>
<th>Eligibility criteria (Insert eligibility criteria for each characteristic as defined in the Protocol)</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
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<td>Type of study</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Controlled Clinical Trial (quasi-randomized trial)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Paediatric patients aged from 4 weeks corrected age to 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of intervention</td>
<td>High flow nasal Oxygen(heated/humidified, flow &gt;2lt/kg/min) Comparator: non invasive respiratory support such as cot/tent/hood, low flow oxygen or CPAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of outcome measures</td>
<td>Hospital mortality; intubation rate; treatment failure. Secondary: duration of any form of respiratory support; length of hospital stay; clinical severity score; length of PICU stay; complications- air leak, nasal trauma, nosocomial sepsis, barotrauma, gastrointestinal distention</td>
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INCLUDE

EXCLUDE

Reason for exclusion

Notes:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Methods
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<th>Aim of study</th>
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<td></td>
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<td>Start date</td>
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<td>End date</td>
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<tr>
<td>Total study duration</td>
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4. **Risk of Bias assessment**

*See Chapter 8 of the Cochrane Handbook (Higgins 2011)*

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(Continued)

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<td>Allocation concealment (selection bias)</td>
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<td>Blinding of outcome assessment (detection bias)</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<tr>
<td>Selective outcome reporting? (reporting bias)</td>
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<tr>
<td>Other bias</td>
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5. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.
6. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1
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<thead>
<tr>
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**Comparison Group 1**

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Comparison Group 2

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<td>(include sufficient detail for replication, e.g. content, dose, components)</td>
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<tr>
<td>Duration of treatment period</td>
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<tr>
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<td>(e.g. frequency, duration of each episode)</td>
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### Delivery (e.g. mechanism, medium, intensity, fidelity)

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### Notes:

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### 7. Outcomes

*Copy and paste table for each outcome.*

#### Outcome 1

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<tr>
<th>Outcome definition (with diagnostic criteria if relevant)</th>
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<table>
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<th>Unit of measurement (if relevant)</th>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Is outcome/tool validated?</td>
</tr>
<tr>
<td>Imputation of missing data (e.g. assumptions made for ITT analysis)</td>
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**Outcome 2**

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<td>Time points reported</td>
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<td>Person measuring/reporting</td>
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Notes:
### Scales: upper and lower limits
(indicate whether high or low score is good)

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| Imputation of missing data
(e.g. assumptions made for ITT analysis) |
|------------------------------------------|

| Assumed risk estimate
(e.g. baseline or population risk noted in Background) |
|----------------------------------------------------------|

### Notes:

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### Outcome 4

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<table>
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<tr>
<th>Unit of measurement (if relevant)</th>
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<tbody>
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<tr>
<td>---</td>
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Outcome 5

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<tbody>
<tr>
<td>Complications- air leak, nasal trauma, nosocomial sepsis, barotrauma, gastrointestinal distention</td>
<td></td>
</tr>
</tbody>
</table>

Time points measured

Time points reported

Outcome definition (with diagnostic criteria if relevant)

Person measuring/reporting

Unit of measurement (if relevant)
### Scales: upper and lower limits (indicate whether high or low score is good)

<table>
<thead>
<tr>
<th>Is outcome/tool validated?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imputation of missing data (e.g. assumptions made for ITT analysis)</th>
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</table>

<table>
<thead>
<tr>
<th>Assumed risk estimate (e.g. baseline or population risk noted in Background)</th>
<th></th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Power</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Notes:</th>
<th></th>
</tr>
</thead>
</table>

#### Outcome 6

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; §/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Hospital stay</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time points measured</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Time points reported</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome definition (with diagnostic criteria if relevant)</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Person measuring/reporting</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit of measurement (if relevant)</th>
<th></th>
</tr>
</thead>
</table>
Scales: upper and lower limits (indicate whether high or low score is good)

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
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</thead>
<tbody>
<tr>
<td>Outcome 7</td>
<td>Clinical severity score</td>
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Notes:
### Scales: upper and lower limits (indicate whether high or low score is good)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</table>

### Is outcome/tool validated?

<p>| | | |</p>
<table>
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<tr>
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</table>

Yes  No  Unclear

### Imputation of missing data

(e.g. assumptions made for ITT analysis)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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### Assumed risk estimate

(e.g. baseline or population risk noted in Background)

<p>| | | |</p>
<table>
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<tr>
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</table>

### Power

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
</table>

### Notes:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

### Outcome 8- secondary outcome

<table>
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<tr>
<th></th>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; §/fig/table)</th>
</tr>
</thead>
</table>

#### Outcome name

Length of PICU stay

#### Time points measured

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

#### Time points reported

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

#### Outcome definition (with diagnostic criteria if relevant)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
</table>

#### Person measuring/reporting

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

#### Unit of measurement (if relevant)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
8. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HFNC</th>
<th>Invasive Ventilation</th>
<th>Non Invasive Ventilation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>with event</td>
<td>No. without event</td>
<td>No.</td>
</tr>
<tr>
<td>Intubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure of Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Continuous outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unit of Measurement</th>
<th>HFNC Group</th>
<th>Invasive Ventilation Group</th>
<th>Non Invasive Group</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M</td>
<td>SD</td>
<td>n</td>
<td>M</td>
</tr>
<tr>
<td>Length of PICU stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Severity Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Respiratory support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 9. Applicability

- **Have important populations been excluded from the study?** (consider disadvantaged populations, and possible differences in the intervention effect)
  - Yes  No  Unclear
- **Is the intervention likely to be aimed at disadvantaged groups?** (e.g. lower socioeconomic groups)
  - Yes  No  Unclear
- **Does the study directly address the review question?** (any issues of partial or indirect applicability)
  - Yes  No  Unclear

### Notes:

---

*High flow nasal cannula therapy for respiratory support in children (Protocol)*

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### HISTORY

Protocol first published: Issue 5, 2012

### CONTRIBUTIONS OF AUTHORS

Conceiving the review: Sara Mayfield (SM)
Co-ordinating the review: SM
Undertaking manual searches: SM
Screening search results: SM and Jacqui Jauncey-Cooke (JJC)
Organizing retrieval of papers: SM
Screening retrieved papers against inclusion criteria: SM and JJC
Appraising quality of papers: SM, JJC and Judith Hough (JH)
Abstracting data from papers: SM and JJC
Writing to authors of papers for additional information: SM
Providing additional data about papers: SM
Obtaining and screening data on unpublished studies: SM
Data management for the review: SM, JJC and Fiona Bogossian (FB)

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<table>
<thead>
<tr>
<th>Description as stated in report/paper</th>
<th>Location in text (pg &amp; ¶/fig/table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusions of study authors</td>
<td></td>
</tr>
<tr>
<td>References to other relevant studies</td>
<td></td>
</tr>
<tr>
<td>Correspondence required for further study information (from whom, what and when)</td>
<td></td>
</tr>
<tr>
<td>Notes:</td>
<td></td>
</tr>
</tbody>
</table>
Entering data into Review Manager (RevMan 5.1): Sara Mayfield
RevMan statistical data: SM and Kristen Gibbons (KG)
Other statistical analysis not using RevMan: KG
Interpretation of data: SM, JJC, FB, JH and Andreas Schibler (AS)
Statistical inferences: SM, JJC, FB and KG
Writing the review: SM
Securing funding for the review: n/a
Performing previous work that was the foundation of the present study:
Guarantor for the review (one author): FB
Person responsible for reading and checking review before submission: JJC, FB, AS and JH

DECLARATIONS OF INTEREST

Sara Mayfield and Andreas Schibler are working on studies with HFNC in the paediatric intensive care unit where they work. To date the trials are observational in nature and not in line with RCTs, however this may change in the future. However, any trial that may be included from these authors will be acknowledged and assessed by an independent person (JH, FB or JJC).

Andreas Schibler: Fisher and Paykel have supported my research by funding one project and supplying equipment in another. Neither projects are published as yet, but may be eligible for inclusion in this review. If any of the studies in the review are deemed to hold a conflict of interest with me, then they will be assessed by an independent person (JH, FB, SM or JJC).

Jacqueline Jauncey-Cooke: none known.
Judith L Hough: none known.
Kristen Gibbons: none known.
Fiona Bogossian: none known.
Appendix 2: Consent for pilot
Parent Information Sheet

Project Title: High Flow Nasal Prong Oxygen Delivery. A pilot study to investigate safety, quality and practicality for a future randomised controlled trial

Investigators:
- A/Prof A. Schibler PICU consultant, Mater Children’s Hospital
- Dr. M. Harris Respiratory and Sleep Medicine, Mater Children’s Hospital
- Dr. C. Dakin Respiratory and Sleep Medicine, Mater Children’s Hospital
- Dr. G. Stone Emergency Department, Mater Children’s Hospital
- Dr. K. McCaffery PICU, Mater Children’s Hospital
- Dr. D. Levitt Paediatrics, Mater Children’s Hospital
- Ms. S. McKee Director of Nursing, Mater Children’s Hospital

We would like to invite your infant to participate in this study. Your infant has a viral respiratory illness (bronchiolitis). Infants with bronchiolitis may need supplemental oxygen. This can be given using a face mask, subnasal prongs or using more invasive means like face mask ventilation or invasive ventilation through a breathing tube inserted into the child’s windpipe. Over the last 5 years we have used in the Paediatric Intensive Care Unit (PICU) a new oxygen delivery system, called, High Flow Nasal Prongs (HFNP) to support work of breathing. We are introducing this method of treatment to the paediatric wards in this hospital. This study aims to assess the quality, safety and practicality of this method in the ward environment.

Why is the study being done?

Respiratory viral illnesses are the leading cause of infants and children requiring hospitalisation. Approximately 8000 admissions occur annually in Australia. The Mater Children’s PICU has been using HFNP since 2005 in infants with viral respiratory illnesses and has shown that it reduces the need to use more invasive means to support the breathing of these patients, such as inserting a breathing tube. It is believed that this mode of treatment can be safely used in the regular paediatric ward environment. This study serves as a pilot study to assess criteria for a larger study, in which the long term benefits of HFNP treatment in bronchiolitic infants will be investigated.

How is the study being done?

There has already been extensive training of staff in the Emergency Department and the paediatric wards to use the HFNP system. As well as training on a HFNP data collection form. This form will assist the ED clinician and nursing staff to safely assess your infants breathing requirements. Once your infant is placed on HFNP (as per protocol), observations of their breathing rate, heart rate and other parameters according to the HFNP form will be taken as per ward policy for the care of an infant with bronchiolitis. A change in score >6 will lead the nurse to seek medical review. From here the treating doctor will decide on treatment as clinically indicated, which may include admission to PICU.
Are there any risks or discomforts?

HFNP is an established form of breathing support for infants with respiratory illnesses in the PICU area. The nasal prongs used for the HFNP treatment are the same as we would use for standard oxygen delivery. Your child will therefore not have any other risks or discomfort. Any change in clinical status on the ward will be reviewed by the treating doctor and arrangements made to transfer to the PICU if needed.

What are the potential benefits?

Although this study will have no direct benefits to your infant, it will help us gain more of an understanding on the effect of HFNP on the respiratory state of this group of infants.

Who will have access to the research records?

Nursing and medical staff in ED, on the wards and in PICU who are involved with this study will have access to the information collected. Your infant’s privacy will be maintained at all times. Your infant’s name will not be used in any presentations or publications of the study results.

Will there be any costs for taking part in the study?

There will be no additional costs for participants in this study.

Do I have to take part in this study?

Your infant’s participation in the study is entirely voluntary. If you decide now, or at a later stage, that you do not wish to participate in this research project, that is entirely your right and will not in any way affect any present or future treatment.

Who do I speak to if any problems arise?

If you are concerned for your infant then you must tell the nurse or doctor caring for them. If you have any concerns about the way in which the research has been carried you, please do not hesitate to contact Sara Mayfield on 31635698.

This study has been approved by the Mater Health Services Human Research Ethics Committee and you may contact the Mater Research Secretariat on 3163 1585, should you have any complaints about the conduct of the research, or wish to raise any concerns. The Research Secretariat may contact the Patient Representative or Hospital Ethicist as its discretion.

Thankyou for your time and consideration of participation in this study.
**Consent Form for Parents or Guardians**

**Project Title:** High Flow Nasal Prong Oxygen Delivery. A pilot study to investigate safety, quality and practicality for a future randomised controlled trial.

**Investigators:**
- A/Prof A. Schibler  
  PICU consultant, Mater Children’s Hospital
- Dr. M. Harris  
  Respiratory and Sleep Medicine, Mater Children’s Hospital
- Dr. C. Dakin  
  Respiratory and Sleep Medicine, Mater Children’s Hospital
- Dr. G. Stone  
  Emergency Department, Mater Children’s Hospital
- Dr. K. McCaffery  
  PICU, Mater Children’s Hospital
- Dr. D. Levitt  
  Paediatrics, Mater Children’s Hospital
- Ms. S. McKee  
  Director of Nursing, Mater Children’s Hospital

- We understand that we have been asked to allow our infant to participate in a study to look at the use of HFNP in the paediatric ward.
- We have read and understood the information sheet.
- The details of the study have been explained to us and our questions have been answered satisfactorily.
- The possible risks and benefits of our infant participating have been explained to us.
- We understand that the project is for the purpose of research and not for treatment, so may not directly benefit us or our child.
- We have been informed that the confidentiality of the information will be maintained and safeguarded and give permission for access to our infants medical records for the purpose of research.
- We give permission for medical practitioners, other health professionals, and hospitals outside this hospital, to release information concerning our infant’s disease and treatment which is needed for this trial and understand that such information will remain confidential.
- We understand that we may withdraw our infant from the study at any time without affecting the care he/she receives.

**CONSENT**

I/We ___________________________________________________________, being the parent(s)/guardians of ____________________________________________ give permission for our baby to take part in this study.

I/We would like to be informed of the study results     NO? ☐ YES? ☐ If yes please provide contact telephone number  ……………………………….

**SIGNED**

(Parent(s)/Guardian(s)) __________________________________________________________________________ DATE

(Signed Witness) __________________________________________________________________________ DATE

(Signed Investigator) __________________________________________________________________________ DATE
Appendix 3: CEWT tool
<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year old</td>
<td>Respiratory rate (breathe / min)</td>
</tr>
<tr>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Respiratory distress
Score
- Moderate
- Nil

O₂ (mmHg) Inform nurse in charge if any |
| > 90 |
| 90 |
| 80 | 70 |

O₂ Saturation (%) Probe change |
| 93 |
| 89 |
| 85 |

Temperature (°C) |
| 40.5 |
| 40 |
| 39.5 |
| 39 |
| 38.5 |
| 38 |
| 37.5 |
| 37 |
| 36.5 |
| 36 |
| 35.5 |

Heart rate (beats / min) |
| 190 |
| 180 |
| 170 |
| 160 |
| 150 |
| 140 |
| 130 |
| 120 |
| 110 |
| 100 |
| 90 |
| 80 |
| 70 |
| 60 |

Blood pressure (mmHg) Score systolic BP |
| 120 |
| 115 |
| 110 |
| 105 |
| 100 |
| 95 |
| 90 |
| 85 |
| 80 |
| 75 |
| 70 |
| 65 |
| 60 |
| 55 |
| 50 |
| 45 |

Capillary refill time | > 2 sec |
| < 2 sec |

Level of consciousness |
| Alert |
| Verbal |
| Pain |
| Unresp. |

Total CEWT Score Interventions |
| 1 |

(Affix patient identification label here)

| URN: |
| Family name: |
| Given name(s): |
| Date of birth: |
| Sex: | M | F | I |

CEWT Score
If an observation moves into one of the shaded areas, add up the patient’s full CEWT score and take action as described in the Actions box below.

Score 0
Score 1
Score 2
Score 3

Actions For rural and remote facilities
Score Action
1–3
- Obtain a full CEWT score
- Carry out and document appropriate interventions as prescribed
- Increase frequency of observations
- Manage anxiety / pain / fever
- Review oxygen requirement
- Consider informing team leader

4–5
- Ward doctor to review within 30 minutes
- Notify team leader
- Obtain a full CEWT score after interventions
- If no review within 30 minutes, escalate to registrar review

6–7
- Registrar to review patient — response within 15 minutes
- If no review within 15 minutes, or if clinically concerned, place emergency call
- Obtain a full CEWT score after interventions
- Registrar to ensure consultant is notified
- Ward doctor to attend

8+
- Place emergency call
- Registrar to attend
- Ensure consultant is notified

Place emergency call if any of the following:
- Airway threat
- Apnoea
- Any observation in the purple area
- Seizure
- You are worried about the patient
You must calculate a full CEWT score:
- on admission
- if patient is deteriorating (increasing score or you are concerned about the patient)

Aside from the above, do appropriate observations at an appropriate frequency for patient's clinical state

For abnormal observations, you must continue to check until normal

Any observations outside the range of the graph, you must write as a number

<table>
<thead>
<tr>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>If abnormal observations are expected for patient's clinical condition, please note below accepted parameters for future calls</td>
</tr>
<tr>
<td><strong>Respiratory rate</strong></td>
</tr>
<tr>
<td><strong>O₂ saturation</strong></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Doctor's name</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doctor's signature</strong></td>
<td><strong>Date</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>If an intervention is administered, record here and note letter in Interventions row over page in appropriate time column</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
<th>N</th>
</tr>
</thead>
</table>

### Pain Assessment Chart Instructions
- Select (with tick) appropriate pain assessment tool
- Plot pain score on graph
- For any score in coloured zone follow instructions in action box
- Note bolus or adjunctive pain relief in table
- If on infusions, use pain infusion chart

### Pain Assessment Tools
Select (with tick) appropriate pain assessment tool

<table>
<thead>
<tr>
<th>Categories</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLACC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suggested age: 2 months to 7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Each category is scored 0-2, resulting in a total score of 0-15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>No particular expression or smile</td>
<td>Occasional grimace or frown, withdrawn, disinterested</td>
<td>Frequent to constant frown, clenched jaw, quivering chin</td>
</tr>
<tr>
<td>Legs</td>
<td>Normal position, or relaxed</td>
<td>Unsteady, restless, tense</td>
<td>Kicking, or legs drawn up</td>
</tr>
<tr>
<td>Activity</td>
<td>Lying quietly, normal position, moves easily</td>
<td>Squirming, shifting back and forth, tense</td>
<td>Arching, rigid, or jerking</td>
</tr>
<tr>
<td>Cry</td>
<td>No cry (awake or asleep)</td>
<td>Moans or whimper, occasional complaints</td>
<td>Crying steadily, screams or sobs, frequent complaints</td>
</tr>
<tr>
<td>Consistely</td>
<td>Content, relaxed</td>
<td>Reassured by occasion touching, hugging, or being talked to, distractable</td>
<td>Difficult to console or comfort</td>
</tr>
</tbody>
</table>

#### Wong & Baker Faces
| Suggested age: 3+ years |
| Point to each face and use words to describe pain |

#### Numerical
| Suggested age: 7+ years |
| Ask child to identify level of pain from scale |

### Pain Assessment Chart
<table>
<thead>
<tr>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actions:</strong></td>
</tr>
<tr>
<td><strong>Pain Score</strong></td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>Q</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>S</td>
</tr>
<tr>
<td>T</td>
</tr>
<tr>
<td>U</td>
</tr>
<tr>
<td>V</td>
</tr>
</tbody>
</table>

### Bolus
Indicate when IV or epidural bolus given

### Enteral
P = Paracetamol  
N = NSAID  
O = Opioid


Appendix 4: MCH HREC approval
MATER HEALTH SERVICES HUMAN RESEARCH ETHICS COMMITTEE

15th February 2011

A/Prof Andreas Schibler
c/- Ms Sara Mayfield
PICU
Level 5
Mater Children's Hospital

Dear A/Prof Schibler

Re: Protocol Ref No. 1639C High Flow Nasal Prong Oxygen Delivery A Pilot Study to investigate Safety, Quality and Practicality for a Future Randomised Controlled Trial.

I write to advise that the Mater Health Services Human Research Ethics Committee considers the above study to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and has granted ethical approval for your research proposal. Please accept our very best wishes for the success of this study. In all future correspondence with the Committee please quote the Mater reference number.

Documents reviewed and approved include:

- Mater Ethics Application dated 11th October 2010
- Study Protocol dated 11th October 2010
- Parent Information and Consent Form dated 11th October 2010
- Staff Information Sheet dated 11th October 2010
- Budget Proposal dated 11th October 2010
- Excerpt of PICU guidelines for High Flow Set Up dated 11th October 2010
- CEWT Tool dated 11th October 2010

This approval is valid until 15th February 2014. Please note the following conditions of approval.

- Any departure from the protocol detailed in your proposal must be reported immediately to the Committee.
- When you propose a change to an approved protocol, which you consider to be minor, you are required to submit a written request for approval to the Chairperson, through the Secretary. Such requests will be considered on a case by case basis and interim approval may be granted subject to ratification at the next meeting of the Committee.
- Where substantial changes to any approved protocol are proposed, you are required to submit a full, new proposal for consideration by the Human Research Ethics Committee.
- You are required to advise the Research Ethics Coordinator immediately of any complaints made, or expressions of concern raised, in relation to the study, or if any serious or unexpected adverse events occur.
- Under the NHMRC National Statement on Ethical Conduct in Research Involving Humans, research ethics committees are responsible for monitoring approved research to ensure continued compliance with ethical standards, and to determine the method of monitoring appropriate to each project. You are required to provide written reports on the progress of the approved project annually, the first report being due on 15th February 2012 and finally on completion of
the project. (The Progress Report is located at http://www.mater.org.au/Home/Research/Human-Research-Ethics-Committee.aspx or can be accessed through the Mater Intranet, Applications, Research Register then under the project name or alternately can be emailed to you). Please inform the Committee of publications, presentations at Conferences, education and quality improvement outcomes from this study. The Committee may also choose to conduct an interim audit of your research.

- Please be aware that all study procedures including follow up of participants and data analysis should be completed within the approval time frame or an extension should be requested.

Please contact the Executive Director in the participating hospital/hospitals prior to commencing of the study. To access medical records, for the purpose of this study, please provide a copy of this approval letter to the Corporate Health Information Manager. I would also be grateful if you could confirm the date of commencement. (All correspondence should be directed to the Mater Research Ethics Coordinator.)

Yours sincerely

[Signature]

Dr Andrew Crowden
Chairperson
Mater Health Services Human Research Ethics Committee
Appendix 5: UQ ethics approval
THE UNIVERSITY OF QUEENSLAND
Institutional Approval Form For Experiments On Humans
Including Behavioural Research

Chief Investigator:  A/Prof Andreas Schibler

Project Title:  High Flow Nasal Prong Oxygen Delivery, A Pilot Study to
Investigate Safety, Quality And Practicality For A Future
Randomised Controlled Trial

Supervisor:  A/Prof Fiona Bogossian

Co-Investigator(s):  Sara Mayfield, Dr Margaret Harris, Dr Carolyn Dakin, Dr
Grant Stone, Dr Kevin McCaffery, Dr David Levitt, Sue
McKee

Department(s):  Medicine, Mater Hospital

Project Number:  2012000618

Granting Agency/Degree:  MCH Golden Casket

Duration:  31st December 2013

Comments:

Expedited review on the basis of approval from the Mater Health Services HREC,
dated 15/02/2011.

Name of responsible Committee:-
Medical Research Ethics Committee
This project complies with the provisions contained in the National Statement on
Ethical Conduct in Human Research and complies with the regulations governing
experimentation on humans.

Name of Ethics Committee representative:-
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Date:  6 June 2012

Signature:  

Appendix 6: MCH HREC amendment
MATER HEALTH SERVICES HUMAN RESEARCH ETHICS COMMITTEE

16th July 2012

Dr Andreas Schibler
Of: Ms Sara Mayfield
Paediatric Intensive Care
Mater Children’s Hospital

Dear Dr Schibler

Re: Protocol Ref #1639C High Flow Nasal Prong oxygen delivery: A pilot study to investigate safety, quality and practicality for a future randomised controlled trial

I write to advise that the Mater Health Services Human Research Ethics Committee has granted ethical approval for the proposed amendments for the above study.

Documents reviewed and approved include:

- Letter dated 21st February 2012 outlining amendment request
- Amendment 21-2-2012 Version 1 tracked
- Amendment 21-2-2012 Version 1 clean

You are reminded that this letter constitutes ethical approval only. You may also need to consult with the Research Governance Office to ensure the amendments comply with the existing authorisation that has been obtained.

Please accept our best wishes for the remainder of the study and should you have any queries, please do not hesitate to contact the Research Ethics Secretariat on 3163 1585. In all future correspondence with the Committee please quote the Mater reference number.

Yours sincerely

A/Prof Andrew Crowden
Chairperson
Mater Health Services Human Research Ethics Committee
Appendix 7: Ward HFNC guidelines
In the Mercy tradition, the Mater will be renowned as a leader in the delivery of exceptional health care through a sincere commitment to the Mater values of:

Mercy, Dignity, Care, Commitment and Quality

Guideline name: High flow therapy for patients with bronchiolitis

Date developed: October 2013

PRINCIPLE: To ensure safe delivery and effective management of high flow therapy for infants under 12 months of age with bronchiolitis at Mater Children’s Hospital (excluding Paediatric Intensive Care Unit).

High flow nasal prong (HFNP) is a system designed to deliver heated humidified oxygen (O₂) at high flows using a specially designed Fisher and Paykel® (F&P) Airvo2 delivery system and circuit with optiflow prongs (OPT 314,316 and 318)

HFNP is a treatment for infants with respiratory distress from bronchiolitis. The effects of HFNP therapy are five fold:

1. It flushes the dead space of the nasopharyngeal cavity allowing for better ventilation as well as oxygenation
2. It provides a flow adequate to support inspiration thereby reducing the inspiratory work of breathing
3. The heated humidified gas improves lung and airway compliance
4. It provides the ability to deliver accurate gas mixtures at body temperature with 100% humidity, thus facilitating mucociliary transport and minimising the viscosity of secretions
5. It can deliver end distending pressure (CPAP)
GUIDELINES:
Initiating therapy in Paediatric Emergency Department (PED) or 8 South:

1. **Inclusion criteria:** Infants with bronchiolitis and an oxygen requirement under the age of 12 months to their birth date.
   a. Oxygen requirement is determined by oxygen saturations.
   b. Work of breathing, while not a direct indicator of oxygen requirement, is nonetheless a marker of respiratory distress, and may contribute to the individual clinicians’ decision making.

2. **Exclusion criteria:**
   a. Infants with choanal atresia
   b. Infants with tracheostomy
   c. Infants with suspected foreign body aspirate
   d. Infants with nasopharyngeal tube

3. Nursing or medical staff may initiate high flow therapy following medical review for the patients that meet the inclusion criteria.

4. All patient’s with high flow therapy will have a nasogastric tube inserted intended for aspiration of air that may accumulate in the stomach.

5. All patient’s with high flow therapy will have access to adequate emergency equipment available at the bedspace.

6. The patient will have the appropriate nasal prongs applied to face and secured with wiggle pads provided.

7. The flow rate will be calculated at 2L/kg/min to a maximum of 25L. If the patient weight exceeds 12.5 kg, commence treatment flow rate at 25L, do not increase beyond 25L in PED or the ward setting.

8. On initial application commence with flow of 6L and gradually increase the flow until **2L/kg** flow is achieved. This increase in flow should be done over 30 seconds – 1 minute. This is because high flows (above...
8L) may initially be uncomfortable for the patient until they adjust to the sensation.

**ALERT**

*In the ward setting*

*The flow rate will not exceed 25L and the FiO₂ will not exceed 60%*

9. The FiO₂ will be commenced at 60% and weaned by 5% increments until oxygen saturations are stable and remain above 93%. **Do not increase the FiO₂ beyond 60% in the PED or the ward setting.**

10. If there is no improvement in oxygen saturations and/or FiO₂ requirement remains greater than 50% within 60 minutes of commencing high flow therapy, a PICU review will be requested. If there is further deterioration, escalate review process as per CEWT actions.

11. It is recognised that weaning to this level make take 1-2 hours, but high flow “responders” can be identified by their initial response to the treatment within the first hour. Consider PICU review if not responding.

12. Once the therapy has been initiated, do **NOT** turn off the flow to assess the patient.

**Transfer from PED to 8 South**

13. The FiO₂ will be less than or equal to 50% prior to transfer to 8 South, this may take up to 1-2 hours to establish.

14. The PED or ward paediatric registrar will review the patient prior to transfer to assess suitability for care in 8 South.

15. The hospital nurse manager/patient flow manager will notify 8 South team leader 30 minutes prior to patient transfer.
16. The nurse allocated to care for the patient in 8 South, will ensure the bedspace is prepared, contact ward services for assistance with transfer, receive handover using the SHARED tool and transfer the patient from PED to 8 South.

17. During the transfer the Airvo2 will not operate without power, leave nasal prongs in situ, apply face mask oxygen 4L and recommence the therapy as soon as able once in 8 South.

Ongoing Management of high flow therapy

The nursing staff will aim to maintain oxygen saturations between 93-98% by titrating the FiO₂ in 5% increments.

18. The patient will be continuously monitored with a pulse oximetry while the high flow therapy is in place.

19. Reassess the patient at least every hour. Continue to decrease FiO₂ if oxygen saturations remain above 98%. Decrease FiO₂ by 5% increments, ensuring oxygen saturations remain between 93% - 98%.

20. If the patient deteriorates or oxygen saturations fall below 93% increase the FiO₂ by 5% increments, ensuring the oxygen saturations remain between 93-98% and escalate review process as per CEWT actions.

21. If FiO₂ requirements increase to greater than 50%. Contact the medical registrar to review the patient within 30 minutes. If the FiO₂ is further increased the PICU registrar must be contacted for patient review within 15 minutes of increased FiO₂. Do not increase the FiO₂ beyond 60% in the ward setting.

22. Minimum of hourly observations will be recorded on the Children’s Early Warning Tool < 1 year and Paediatric Respiratory Observation Chart.
23. Feeding Requirements

Feeding regime as per medical plan

a. The infant may feed orally or enterally as indicated by condition, refer to guideline: Acute Bronchiolitis Management in PED - MHC-WCH-C-142.

b. Shorter/smaller volume more frequent oral feeds should be trialled first, if not tolerated, trial bolus feed via nasogastric tube. If there is respiratory deterioration with bolus feeds, consider continuous nasogastric feeds until improvement in patient condition.

c. Aspirate the nasogastric tube prior to each feed or 4th hourly if continuous nasogastric feeds are being administered.
   i. To check the tube placement
   ii. To reduce air that may cause abdominal distension

24. Observations

a. The infant will have continuous heart rate and oxygen saturation monitoring via pulse oximeter and oxygen saturation monitor.

b. Document minimum of hourly respiratory rate, respiratory distress, oxygen saturations, heart rate on the Child Early Warning Tool <1 year old (CEWT).

c. Document other observations on the CEWT as patient condition dictates.

d. Document hourly respiratory assessment on the Paediatric Respiratory Observation Chart

e. Document hourly high flow therapy system checks on the Paediatric Respiratory Observation Chart, including FiO₂, flow rate, water check.

f. Visual check of nasal prong position and observe skin integrity around nasal prongs.

g. Patients requiring radiological investigations should remain in PED/8 South if possible, to avoid ceasing and recommencing therapy.

25. Patient handling and other cares

a. Provide a restful environment for the infant, consider grouping cares and minimal handling as appropriate.

b. Provide oral hygiene minimum of every 4-6 hours if patient is nil by mouth.
c. Provide pressure area cares as directed by the risk assessment conducted each shift.

d. Reposition oxygen saturation probe 2-4 hourly or more frequently if required.

### 26. Suctioning & 0.9% Sodium Chloride

a) Maintain airway patency with nasal suctioning to clear excessive nasal secretions. Consider that suctioning may cause oedema and further irritate the airway.

b) Sodium chloride drops or atomised sodium chloride are not required due to humidification provided by the circuit.

### 27. Rapid clinical deterioration

a. Follow the actions on the CEWT

b. Call for help, initiate Medical Emergency Team (MET) call.

c. Bag and mask breaths can be delivered while the nasal prongs remain insitu.

### 28. Weaning high flow therapy

a. Wean FiO\textsubscript{2} to 21%

b. Once weaned to 21%, continue to observe patient for 4 hours while at this treatment flow

c. If patient is stable turn off the flow – do not wean the flow rate

d. Clinical signs the patient is stable include:
   i. Decreased work of breathing
   ii. Normal or improved heart rate
   iii. Normal or improved respiratory rate
   iv. Saturations above 93%

e. If patient has pre-existing oxygen requirement, an individualised weaning plan must be documented by the medical officer in the medical notes.
   i. Recommendation is to wean to 25% FiO\textsubscript{2} at treatment flow, observe the patient for 4 hours, if stable, convert to low flow at pre-existing oxygen requirement flow.

### 29. Deterioration post high flow therapy wean

a. If after high flow therapy has been weaned the patient has an increased work of breathing or oxygen saturations fall below 93%, consider re-initiation of high flow or low flow oxygen therapy.
b. If recommencing on high flow oxygen commence at initial treatment flow rate and $\text{FiO}_2 - 21\%$, increase $\text{FiO}_2$ by $5\%$ increments to keep oxygen saturations above $93\%$

c. Request medical review

**Appendix 1**

Each cot space will be equipped with a 15L flow meter and will be attached to the Airvo2.

1. **Components of System:**
   1. 900PT531 circuit
   2. Nasal Prong
   3. F&P MR850 Humidifier base (only this base is compatible)
   4. Water Bag
   5. Oxygen tubing

A. Prong selection:
   i. The following parameters should be utilised when selecting nasal cannula.
      1. OPT 314 for neonates, with flow limited at 8L/min
      2. OPT 316 for infants to 20L/min
      3. OPT 318 for infants/paeds to 25L/min

2. **Set Up:**

   A. Select appropriate size nasal prong, and connect to adaptor on circuit, connect the circuit to the Airvo machine.

   B. Place the chamber in the Airvo machine and attach water bag. The water bag must run freely and be placed as high as possible above the humidifier to achieve flow of water into the humidifier chamber.

   C. Turn the Airvo2 machine on and adjust the flow rate to the prescribed rate

   D. Ensure Airvo2 is attached to oxygen outlet, adjust the oxygen flow rate to achieve desired oxygen concentration.
E. Wiggle pads used to secure the prongs to the patients face and can be replaced as needed, particularly for the patient with moderate to large secretions.

F. System is ready for use.

LINKS:

MHS-WCH-C-079 Oxygen Therapy
http://MatDCS/DocCube/default.asp?Id=5306

MHS-WCH-C-086 Humidification Guidelines
http://MatDCS/DocCube/default.asp?Id=3892

REFERENCES:


**KEYWORDS:** nasal prongs, high flow, oxygen therapy