

Non-Invasive Ventilation during Paediatric Retrieval: A Systematised Review

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Declaration

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Abstract

Non-Invasive Ventilation during Paediatric Retrieval: A Systematised Review

Background: In hospital critical-care and emergency settings, non-Invasive ventilation (NIV) is increasingly used in neonatal and paediatric patients as an alternative to invasive positive pressure ventilation (IPPV). Critically ill children and babies may need transfer to higher levels of care, but the emergency transport setting is lagging behind the hospital sector in terms of availability of NIV.

Aim and objectives: The goal of this study was to assess the evidence on the safety and effectiveness of NIV in children during transportation. Safety outcome measures were intubation or escalation of ventilation mode (during and soon after transport) and adverse event (AE) occurrence during transport. Effectiveness outcome measures related to improvement in clinical parameters during transfer.

Methods: A systematised review of the literature was conducted, based on searches of MEDLINE via PubMed, EMBASE (via Scopus), Cochrane Central Register of Controlled Trials (CENTRAL), African Index Medicus, Web of Science Citation Index and the World Health Organisation Trials Registry (ICTRP). Two reviewers independently reviewed all identified studies for eligibility, with an initial screening round followed by a full-text review of potentially relevant articles. The quality of studies meeting inclusion criteria was evaluated using an adapted quality assessment tool developed for this study.

Results: A total of 1287 records were identified; of these, 12 studies met inclusion criteria. Following quality assessment, eight studies were included and four studies were excluded. There were no randomised controlled trials, quasi-randomised controlled trials or non-randomised studies of intervention, to answer the research question. The included studies were all observational in design: seven studies (n= 708) evaluated in-transport use of continuous positive airway pressure (CPAP) and one study (n=150) reported on use of high-flow nasal cannula (HFNC) in children during transport.

During transport on NIV, 3/858 (0.4%) patients required either intubation (1/708; 0.1%; CPAP studies) or escalation of mode of ventilation (2/150; 1%; HFNC study). In the 24 hours following transfer, 63/650 (13%) of children transferred on NIV, were intubated. The odds of intubation within 24 hours were significantly higher for CPAP transfer 60/500 (12%) compared with HFNC 3/150(2%): OR (95% CI) 6.68 (2.40 – 18.63), p=0.00003.

Adverse events, where reported, were found to occur in 2-4% of NIV transports, with use of BVM in 8/334 (2%), desaturation episodes in 9/290 (3%), apnoea in 11/290(4%) and administration of CPR in 0/290 (0%) cases being described. There was insufficient reporting of change in vital signs or clinical condition during transport for meaningful analysis.

Conclusion: This study is the first systematised review indicating that NIV use in children during transport is likely to be safe. From the low-reliability evidence available, it was calculated that NIV use in children during transport would result in a 0.4% rate of intubation or escalation during transport and an in-transport adverse event rate of 2-4%. There was insufficient evidence to comment on clinical effectiveness of NIV during transfer. Following NIV transfer, 13% of patients were intubated within 24 hours, with significantly higher odds of intubation in children transported on CPAP compared with HFNC.

Recommendations: Further research is needed in order to make firm recommendations regarding the safety and effectiveness of NIV during transport of children. A recommended minimum data set, for the standardised reporting of observational studies of paediatric NIV use during transport, is suggested. It is recommended that transport databases and registries are expanded to include NIV details as well as information regarding the presence or absence of pre-specified adverse events during transport.

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Abbreviations

B _u CPAP	Bubble continuous positive airway pressure
CI	Confidence interval
CLD (=BPD)	Chronic lung disease (synonym = Bronchopulmonary dysplasia)
CO ₂	Carbon dioxide
CPAP	Continuous positive airway pressure
CrI	Credible interval
EMG	Electromyography
EPAP	Expiratory positive airway pressure
ETT	Endotracheal tube
FiO ₂	Fractional inspired oxygen
FRC	Functional residual capacity
HFNC	High-flow nasal cannula
HTA	Health technology assessment
IFD	Infant flow-driver
IFT	Inter-facility transport
IPAP	Inspiratory positive airway pressure
IPD	Independent patient data
IPPV	Invasive positive pressure ventilation
LFNC	Low flow nasal cannula
MV	Minute ventilation
NAVA	Neurally-adjusted ventilatory assistance
NICU	Neonatal intensive care unit
NIV	Non-invasive ventilation
NNTB	Number needed to treat to benefit
NNTH	Number needed to treat to harm
NPV	Negative pressure ventilation
O ₂	Oxygen
PaCO ₂	Arterial partial pressure carbon dioxide
PaO ₂	Arterial partial pressure oxygen
PARDS	Paediatric Acute Respiratory Distress Syndrome
PEEP	Positive end expiratory pressure
PICU	Paediatric intensive care unit
QA	Quality assessment
RCTs/QRCTs	Randomised or quasi-randomised controlled trials
RT	Retrieval team
Ti	Inspiratory time
T _v	Tidal volume
VILI	Ventilator-induced lung injury

CHAPTER 1: INTRODUCTION

What is the problem and why is it important?

Infants and young children, due to the anatomical and physiological immaturity of their respiratory and immune systems, are at increased risk of developing acute respiratory failure (ARF).(1–3) Assisted ventilation is usually required by patients with established or impending ARF; this support may be delivered by invasive means (with indwelling endotracheal tube, ETT) or non-invasively (without ETT). For the purposes of this study, two main categories of non-invasive ventilation (NIV) will be considered: non-invasive continuous positive airway pressure (CPAP) and high-flow nasal cannula (HFNC) therapy.

Non-invasive ventilation is increasingly preferred to invasive positive-pressure ventilation (IPPV) in paediatric and neonatal hospital settings because of the avoidance of risks associated with intubation and IPPV.(1–6) The problem is that NIV use in children in the pre-hospital transport setting has been less widely reported.(7,8) This means children being managed on NIV who require transfer to another facility may end up being intubated and placed on IPPV just for the journey. This negates the attempts to avoid intubation and IPPV risks, and it would be ideal for transport services to offer NIV during transport of children.

What is known – in brief?

The majority of high-quality randomised controlled trial (RCT) evidence on NIV use in children comes from the neonatal intensive care unit (NICU) settings. There is a gradually increasing body of research being done in paediatric intensive care unit (PICU) and emergency department (ED) settings, albeit that high-quality RCT data is still not available from these environments.

This research on the whole shows that CPAP may reduce the need for IPPV, and in certain circumstances HFNC is equivalent to CPAP in this regard, but that overall there is insufficient evidence on HFNC use to draw conclusions. There is increasing evidence that newer modalities of CPAP, using bi-level pressures, may be more effective than traditional CPAP. The major drawbacks of NIV are related to two main categories of adverse effect: air leaks and local pressure problems. See Chapter 2: Literature Review, for a more detailed presentation of the research evidence regarding clinical effectiveness of NIV use in neonates and children.

There is sufficient RCT evidence of NIV use in adults in pre-hospital transport settings to permit systematic review and meta-analysis, which suggests that NIV in transport reduces

mortality and intubation rates.(9,10) However, research on the use of NIV in children in transport settings is still sparse and is the subject of this review.

What will this study add?

This study systematically searched for available research on NIV use during inter-facility transport of children with acute respiratory distress and evaluated this for evidence of safety and effectiveness of NIV during transportation. This information is currently not available and will assist clinicians, researchers and healthcare managers with decisions regarding the value of NIV use during inter-facility transportation of children.

In addition a comprehensive literature review is presented under the following headings:

- **The condition:** this section provides an overview of lung dynamics and respiratory physiology that predispose infants to ARF, as well as a brief review of respiratory failure terminology and classification.
- **The intervention:** this section describes the evolution of mechanical ventilation and overviews some of the risks associated with IPPV. This is followed by an explanation of the various types of NIV, divided broadly in to CPAP and HFNC. Further detail is provided on the mechanism of action, methods of generation and settings used for CPAP and HFNC. The section ends with a consideration of the literature on matters such as NIV interfaces, synchronisation and adverse effects.
- **Clinical effectiveness:** systematic review (with or without meta-analysis) is relied upon in this section, which reviews the evidence on clinical effectiveness of NIV. The focus is on NIV use in neonatal populations, due to the predominance of research on this group. There is additional review of NIV use in paediatric acute respiratory distress and HFNC clinical use in children.
- **The setting:** the transfer critically ill neonates and children presents its own special challenges. Those relevant to NIV use during transport will be discussed in this section.

How was this study done?

A rigorous review methodology, based on the Cochrane collaboration systematic review methodology(11), was used. This review is labelled as a 'systematised review' as opposed to a 'systematic review' on the basis of the typology and classification of reviews recommended by Grant & Booth.(12)

A detailed research question was delineated, with pre-specified primary and secondary objectives – see Chapter 3: Research Questions, Study Aims and Objectives. The search phase involved a comprehensive systematic search with the assistance of a research librarian. Pre-defined search terms were used to search a broad range of relevant databases and trials registries. This was followed by a selection process involving two independent reviewers, reviewing titles for pre-defined inclusion and exclusion criteria, with a full-text review of any potentially relevant studies. Data was extracted independently by two researchers and analysed with the assistance of a statistician. See Chapter 4: Methodology for full details of study methods. The results are presented in a manner that addresses the research questions through the primary and secondary objectives – see Chapter 5: Results for full details.

How were studies assessed for quality?

Following the selection process, it became apparent that all included studies were observational studies. These were primarily of cohort type design, with a variety of mainly, retrospective record review and database search methods used. Details of study methodology, as well as the scope and depth of reporting of outcomes, was variable.

Quality assessment (QA) tools are available for a number of study designs (see Appendix A), however, few are suitable for comparison of retrospective, record and database review studies, with a moderate degree of variation in reporting. For this reason a QA tool was adapted for use in this study. The evolution of the original tool is described in detail in Appendix A and the original tool is available in Appendix B. The process of adaptation is described in Chapter 4: Methodology and the adapted tool is presented in Appendix C.

Was the study able to answer the research question?

The study was able to provide an answer to half of the research question: the results of this review suggest that use of NIV during inter-facility transport of children, is likely to be safe, because of low rates of intubation, escalation of ventilation and AEs during transport. However, this finding was based on low-reliability evidence, and must therefore be interpreted with caution. This study was unable to answer the research question with respect to clinical effectiveness of NIV during the transport of children, due to a lack of data on these parameters, in the included studies. See Chapter 6: Discussion and Chapter 7: Implications, Conclusion and Recommendations for full details.

CHAPTER 2: LITERATURE REVIEW

The Condition

This section provides an overview of lung dynamics and respiratory physiology that predispose infants to ARF, as well as a brief review of respiratory failure terminology and classification.

Respiratory physiology predisposing infants to acute respiratory failure

Lung dynamics

The functional residual capacity (FRC) is the volume of air left in the lungs at the end of exhalation, and this is where gas exchange takes place.(2) The FRC is determined by the balance between the elastic recoil of lung tissues and the outward pull of the chest wall. (1,2) Healthy adults and older children with rigid rib-cages and compliant lungs are able to maintain FRC due to a fair balance between these forces. New-born babies and small infants have comparatively weak chest walls that suck inwards as a result of a stronger pull of stiffer lungs, leaving them with a relatively lower FRC. (1,2)

In order to keep FRC above the volume at which the smaller airways begin to close, infants rely on strategies such as laryngeal braking (partial close of larynx to retain end expiratory air); contraction of inspiratory muscles during exhalation (to maintain chest volume); and a shortened expiratory phase (to limit air escape).(1) This is a delicate balance, which can easily be disturbed at times of respiratory infection or other systemic upset.

Respiratory mechanics

Compared to those of adults, infant chest wall structures are more pliant, the ribs are more horizontal, and the intercostal muscles contribute little to chest expansion; this means that infants are more reliant on diaphragmatic excursion to generate negative pressures to draw air into the lungs.(1,2) In adults, the main resistance to airflow is from upper airway structures, but in children under five years of age, most resistance is found in the small peripheral airways.(2) These airways are considerably smaller than those of adults or older children and they become more easily narrowed by the presence of mucus, exudates or swelling of the cells lining the airway.(2)

Work of breathing

The main work of breathing (WOB) occurs during inspiration, when intercostal and diaphragmatic muscles contract to expand the chest.(1) Exhalation is normally passive, but may become active in disease states with increased resistance to expiratory airflow.(1) In infants the diaphragm contains fewer Type 1 muscle fibres than in adults, and this makes it more susceptible to fatigue.(1)

The WOB may increase in situations where the lungs become stiffer or the resistance to airflow increases.(2) New-born babies (especially those with surfactant deficiency) and small infants have relatively stiff lungs compared to older children and adults.(1,2) Decreased lung compliance can also occur in older infants and children with infected, collapsed or fluid-filled lungs.(1,2) The smaller size of infant airways, and the propensity of their lumina to narrowing during disease processes, can result in huge increases in the work of breathing. According to Poiseuille's Law(13), a 50% reduction in diameter results in 16 times higher resistance and will require a great deal more energy to overcome, in order to get air into the alveoli.(2)

Respiratory failure terminology

Many terms are used to describe children with signs and symptoms of respiratory system impairment. However, little agreement exists on exact criteria and definitions.(14) Recent advances have been made regarding criteria for defining adult acute respiratory distress syndrome (ARDS)(15), but there are conflicting proposals regarding the application of these criteria to children.(16–19)

Figure 1: Definition of acute respiratory failure

Respiratory failure results when the pump function of the respiratory muscles can no longer sustain a threshold level of alveolar gas exchange to meet the metabolic demands of cellular respiration.

Source: Teague, GW, Noninvasive ventilation in the pediatric intensive care unit for children with acute respiratory failure.(3)

For the purposes of this review, the term 'acute respiratory distress' will be used in a broad sense to denote children suffering acute respiratory compromise from a variety of pathologies, with the latter covering the spectrum from mild to moderate disease. The term

'acute respiratory failure' (ARF) will be defined as in Figure 1 and used to describe children with more severe diseases that require assisted ventilation.¹

Respiratory failure

Acute respiratory failure in children tends to be primarily acute hypoxic respiratory failure (Type 1) with low PaO₂ and normal-low PaCO₂, whereas Type 2 ARF is characterised by hypoventilation with high PaCO₂, with or without low PaO₂. Patients in whom the respiratory muscles start to fail can transition from Type 1 to Type 2 ARF.⁽²⁰⁾ Provision of additional fractional inspired oxygen (FiO₂) will only assist with hypoxia. Reducing the arterial partial pressure of carbon dioxide (PaCO₂) requires improved gas exchange through enhanced ventilation.^(3,5) This involves some form of assisted mechanical ventilation to increase FRC and ideally also increase tidal volume (TV) and minute ventilation.^(2,3)

¹ However, when describing findings from specific studies, the terms and definitions used by the authors will have to be relied on.

The Intervention

This section of the literature review describes the evolution of mechanical ventilation and overviews some of the risks associated with IPPV. This is followed by an explanation of the various types of NIV, divided broadly in to CPAP and HFNC. Further detail is provided on the mechanism of action, methods of generation and settings used for CPAP and HFNC. The section ends with a consideration of the literature on matters such as NIV interfaces, synchronisation and adverse effects.

Evolution of mechanical ventilation

Whilst it was recognised as far back as the sixteenth century that application of positive pressure through the trachea could be used for resuscitation (see Figure 2), a lack of suitable materials and technology meant that any form of assisted ventilation was slow to evolve.(21) Initial attempts at mechanical ventilation centred around the use of negative pressure to expand the patient’s lungs externally; as will be described, there has been a cycle from initial use of non-invasive ventilation (NIV) towards invasive positive-pressure ventilation (IPPV) and more recently back to NIV.

Figure 2: Observation by Andreas Vesalius

“But that life may be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and take air” – Andreas Vesalius (1514-1564)

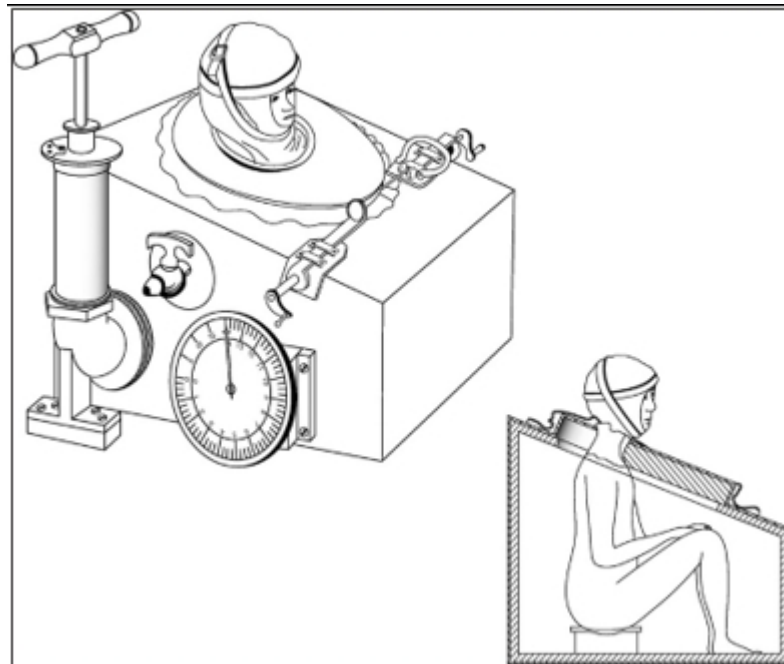
Source: Quoted in Slutsky, AS History of Mechanical Ventilation. From Vesalius to Ventilator-Induced Lung Injury.(21)

Negative pressure ventilation

Isolated reports of externally applied mechanical ventilation began to appear in the mid-nineteenth century. These mostly involved body-enclosing chambers (with the head and neck outside of the chamber) attached to manual bellows or plunger devices, which were used to generate pressure variations (see Figure 3).(21,22)

The first functional negative pressure ventilation (NPV) ‘respirators’ or ‘iron-lungs’ were developed in the late 1920s. These still consisted of whole-body negative pressure chambers, but now with the benefit of electricity to produce sub-atmospheric pressures.(21,23) These respirators proved useful during the poliomyelitis epidemics of the 1930s and 1940s for the 10% of patients who presented with respiratory muscle paralysis.(23)

Figure 3: Example of a body-enclosing box (patented by Alfred Jones in 1864)



Copied from: Slutsky, AS History of Mechanical Ventilation. From Vesalius to Ventilator-Induced Lung Injury(21)

Invasive positive pressure ventilation

The turning point came during the Danish polio epidemic of 1951, which may have been caused by viral transmission during the Copenhagen international polio congress of 1950.(21) Due to a lack of sufficient NPV devices, during this epidemic patients with respiratory failure secondary to muscle paralysis were treated with tracheostomy followed by positive-pressure ventilation. This rapidly became the technique of choice after it was shown that mortality fell from 87% to 40% using this approach.(21) Unfortunately, a lack of positive-pressure generating ventilators meant that patients had to be hand-ventilated: 1500 medical students are said to have provided 165,000 hours of manual ventilation during this epidemic.(21)

Shortly thereafter, ventilators designed specifically to administer IPPV became available and custom-made consumables were developed. This heralded an era in which IPPV became the mainstay of assisted mechanical ventilation.(21)

Harm associated with Intubation

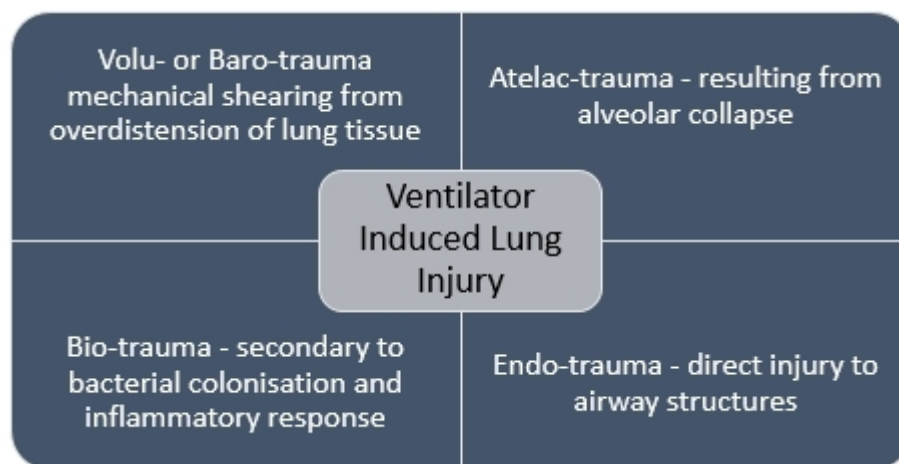
Well-recognised risks are associated with the process of inserting the endotracheal tube (ETT), including hypoxia, damage to airway structures, oesophageal or right main bronchus placement and cardiovascular collapse following rapid-sequence induction (RSI).(2,24) These

risks are higher in a transport settings due to the limited availability of advanced airway equipment, the restricted access to drugs, shortage of space and, depending on the team composition, lack of highly specialised airway skills.(25–27)

Ventilator-induced lung injury

Although materials, technologies and techniques have become more sophisticated since the early days of IPPV, it has been increasingly recognised that direct transmission of positive pressure to the lungs has an inherent risk of harm.(2,6,28) Ventilator-induced lung injury (VILI) is the umbrella term used to describe the negative effects of IPPV on the lungs caused by variety of interacting mechanisms (see Figure 4).

Figure 4: Proposed mechanisms of ventilator-induced lung injury



Source: Adapted from Mahmoud et al. Current methods of non-invasive ventilatory support for neonates.(6)

VILI effects are more pronounced in vulnerable groups such as small infants, neonates and premature babies.(6) In these groups, the mere presence of an ETT is associated with infection, with 80% showing tracheal colonisation within a few days of intubation.(29) These patients have immature respiratory systems with evolving structures that can be severely damaged by IPPV. Bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) are two well-known adverse effects of IPPV in surviving premature infants.(30)

Non-invasive ventilation

As early as 1914, new-born infants with respiratory difficulty were being treated with a form of liquid-seal continuous positive airway pressure (CPAP) administered by facemask in Germany (as described in 23). However, it was almost 60 years before modern CPAP devices began to be described for use in children.(21,32).

The objectives of NIV in paediatric patients have been summarised as decreasing the WOB; reversing hypoventilation; increasing FRC; and maintaining upper airway patency (see Table 1). To this list can be added avoiding the harms of intubation and IPPV.

Table 1: Benefits of non-invasive ventilation in paediatric patients with respiratory disorders

Decrease work of breathing	<ul style="list-style-type: none"> • ‘Unload’ diaphragm and accessory muscles of breathing • Decrease respiratory rate • Stabilise chest wall and thus decrease retractions • Decrease oxygen consumption associated with breathing
Reverse hypoventilation	<ul style="list-style-type: none"> • Increase tidal volume and minute ventilation • Decrease arterial and end-tidal PaCO₂
Increase functional residual capacity	<ul style="list-style-type: none"> • Decrease alveolar-arterial oxygen tension difference • Prevent atelectasis • Decrease auto-PEEP
Maintain upper airway patency	<ul style="list-style-type: none"> • Decrease number and length of occlusive apnoeas and hypopnoeas

Copied from:: Non-invasive Ventilation in the Pediatric Intensive Care Unit for Children With Acute Respiratory Failure, Teague, WG.(3)

Definition and terminology for non-invasive ventilation

The terms used to describe NIV in the literature are not standardised: a wide variety of labels and acronyms are used to describe the same or very similar NIV modalities.(2,6) The NIV definitions and terminology that will be used for this study are outlined in Table 2.²

² Note that this table was created by Baljit Cheema for this dissertation.

Table 2: Definitions and terminology for non-invasive ventilation

Group terms	Acronym (Synonyms)	Full label	Description	
NON-INVASIVE VENTILATION	CPAP	CPAP	Standard Continuous Positive Airway Pressure	Pressure is delivered at a set steady level throughout the respiratory cycle. Pressure supplied is higher than compared with intra-thoracic pressure during exhalation, but lower during inhalation. CPAP is generally a closed system, requiring a tight seal at the patient interface.
	CPAP DERIVATIVES	B _u CPAP	Bubble CPAP	Expiratory limb placed in water which creates pressure by resistance to gas flow equivalent to the height of the column of water.
		B _i PAP (BiPAP, SiPAP)	Bi-level Continuous Positive Airway Pressure	Continuous positive airway pressure is supplied at two levels: lower and higher pressure. Breaths are taken at lower level followed by gradual transition up to higher level. Can vary duration at each level. Change of CPAP level may be synchronised or not.
		SNIPPV/ NIPPV (NI-PSV)	(Synchronised) Non-Invasive Positive Pressure Ventilation	On top of background CPAP, a set number of ventilator-type breaths are available to be delivered to the patient non-invasively. Depending on device: <ul style="list-style-type: none"> • Settings may include: PIP, PEEP, rate & T_i • May be pressure- or volume-controlled • Breaths may be synchronised or not • Backup rate may be available • Degree of compensation for leak at interface
		SNIMV/ NIMV/	(Synchronised) Non-Invasive Intermittent Mandatory Ventilation	A set number of ventilator-type inspiratory breaths (with pre-set PIP, PEEP, rate & T _i) are delivered on background CPAP. These breaths are delivered regardless of the patient's respiratory performance. May be pressure- or volume-controlled with or without synchronisation.
HFNC	HFNC (HF, HHFNC/P, HHHFNC/P)	High-flow Nasal Cannula Oxygen therapy	Unidirectional flow of blended oxygen-air mixture, heated to body 37 ⁰ C and 100% humidified. Delivered at higher than normal flow rates, via loose-fitting prongs. Heated and/or insulated circuits commercially available to optimise heat/humidity delivery.	

Some authorities classify HFNC as a type of CPAP(32), whilst others consider it a separate entity(1,2); for the purposes of this review, CPAP (and its derivatives) will be considered separately from HFNC oxygen therapy. It should be noted that a recurrent problem with evaluating the literature on NIV is that studies in this domain use a variety of devices, pressure/flow settings, interfaces, patient groups and clinical environments, sometimes making meaningful comparison between studies difficult.(1,2,32,33)

Continuous positive airway pressure

What is non-invasive continuous positive airway pressure

Continuous positive airway pressure involves the provision of a set background level of positive pressure to the patient's airways throughout the respiratory cycle. Using standard CPAP, pressure is supplied at one set pressure during the entire respiratory cycle. Newer modalities have additional options, such as two set levels of pressure, delivery of ventilator-type breaths and synchronisation with respiratory phase (see Table 2).(2,3,32)

Mechanism of action

In patients with respiratory compromise, the application of CPAP to the airway has a variety of potentially beneficial effects (see Table 1), including increased FRC through maintenance of the patency of smaller airways and recruitment of alveoli; improved pulmonary blood flow and ventilation-perfusion matching; and reduced respiratory muscle workload.(1,2) Bi-level CPAP further enhances T_v and minute ventilation (MV), leading to improved carbon dioxide (CO_2) clearance.(1,2) In preterm infants, CPAP helps preserve surfactant and reduces obstructive, but not centrally-mediated, apnoea.(1,2)

Methods of continuous positive airway pressure generation

Continuous positive airway pressure can be generated by continuous or variable gas flow and may result in constant or variable pressure.(1,2,32)

Continuous flow mechanisms

- Expiratory flow valve – a valve in the expiratory limb of a mechanical ventilator is adjusted to impede expiratory gas flow resulting in positive pressure to be experienced throughout exhalation. The valve may be controlled manually or be servo-controlled in response to patient parameters. (1,2)

- Liquid seal – the expiratory limb of the CPAP circuit is placed under liquid (usually water), with the depth of submersion of the tip determining the amount of pressure experienced during exhalation. Bubbling occurs as a result of gas flow being passed through the circuit; loss of bubbling indicates a leak in the system. Some argue that the bubbling causes rapid pressure oscillations which further enhance gas exchange and ventilation(34), but others maintain that any such oscillation dissipates before reaching the alveoli.(35)

Variable flow mechanism

- Fluidic flow-opposition – gas jets are passed through apertures within CPAP generator devices close to the interface with the patient airway. Pressure is generated based on mechanisms that rely on Bernoulli’s theorem, which states that slowing down the movement of a fluid (liquid or gas) will result in it generating an increased pressure (this is also known as the Venturi effect).(32,36) Variable flow rates, dependent on the milieu of the patient’s upper airway, are used to provide constant pressure. These devices have been shown to provide more consistent constant pressure than constant flow CPAP devices.(32)

Continuous positive airway pressure settings

Table 3: Changes in respiratory and lung parameters with increasing CPAP level

	0cm	2cm	4cm	6cm	8cm
Respiratory rate	70 ± 12	50 ± 15	55 ± 12	52 ± 17	45 ± 18
EELV	0	38 ± 25	110 ± 46	135 ± 49	210 ± 37
Tidal volume	99	104 ± 10	110 ± 18	125 ± 20	143 ± 24
Phase angle	76 ± 21	63 ± 25	54 ± 19	36 ± 27	30 ± 15

EELV, end expiratory lung volume. Note: Phase angle is a measure of thoraco-abdominal asynchrony.

Source: Elgellab et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature new-born infants.(37)

Despite its having been in clinical use since for more than 45 years, there is little evidence to guide the optimal CPAP settings in children.(5,6,33) In the initial study of CPAP in neonates, CPAP pressure of 12mmHg (16cmH₂O) was used (38), but it now seems to have become standard to commence CPAP at pressures of 3-5cm, with usually suggested maximum pressures of approximately 10-12cm guided by clinical response.(4,5,30,33) In the absence

of good evidence, it is difficult to understand how the standard lower pressures have been agreed upon.

Evidence suggests that higher CPAP pressures lead to improvement in a range of lung parameters (see Table 3)(37,39) and reduction of treatment failure in neonates.(40,41) However, there is also concern that higher pressures may be linked to an increased incidence of air leak complications (see Clinical effectiveness of NIV in children).(41,42)

High-flow nasal cannula oxygen therapy

What is HFNC?

Warmed and humidified gas is provided through nasal prongs: heating to body temperature (37°C) and humidifying to 99-100% of relative humidity of inspired gases permits use of much higher flow rates than when using cold and/or dry low-flow nasal cannula (LFNC) oxygen.(43,44)

Low-flow versus high-flow

There seems to be no agreement in the literature on the upper margin of LFNC and what should qualify as HFNC. Some authors define high-flow as being any flow rate over 1L/min(44,45) and others over 2L/min(2), whilst some argue that nothing less than 4L/min is effective.(43)

Mechanism of action

The mechanism of action of HFNC is not well understood, but a variety of potential mechanisms have been proposed (see Figure 5).(1,2,43,44) The unidirectional high flow of gas is thought to effectively clear CO₂ from the upper airway, in addition to having a stenting effect on the collapsible upper airway structures.(46) The warmth and humidity of inspired gases is postulated to improve gas flow dynamics as well as reduce metabolic energy expenditure.(46) It is clear that HFNC imparts a variable and unpredictable amount of positive pressure to the airway (see the section further below on the magnitude of distending pressure).(32,44)

Method of high-flow nasal cannula generation

A blend of oxygen and air is passed through a heating and humidifying unit and then conducted to the patient. (1,2,43,44) Some commercially available HFNC devices use specially designed heated and insulated circuits to optimise transference of the generated

heat and humidity to the patient.(32) High-flow nasal cannula oxygen therapy has also been described using non-commercial methods, in low-resource settings using oxygen from oxygen concentrators passed through room temperature humidifiers, at higher than normal flow rates, and using flexible, low-resistance nasal prongs.(47,48)

Figure 5: Proposed mechanisms of action of HFNC

<p>1. Washout of nasal deadspace</p> <p>HFNC provides for washout of nasopharyngeal dead space, which contributes to establishing improved fraction of alveolar gases with respect to carbon dioxide as well as oxygen.</p>
<p>2. Decreased nasopharyngeal resistance</p> <p>The distensibility of the nasopharynx provides significant resistance on inspiratory relative to expiratory efforts. HFNC provides adequate flow rates to match inspiratory flow and thus markedly attenuates the inspiratory resistance associated with the nasopharynx, thereby eliminating related work of breathing.</p>
<p>3. Improved gas flow dynamics</p> <p>The provision of adequately warmed and humidified gas to the conducting airways improves conductance and pulmonary compliance compared to dry, cooler gas.</p>
<p>4. Reduced metabolic work</p> <p>The provision of adequately warmed and humidified gas through the nasal pharynx reduces the metabolic work associated with gas conditioning.</p>
<p>5. Positive distending pressure</p> <p>High flow through the nasopharynx can be titrated to provide positive distending pressure for lung recruitment.</p>

Source: *Dysart, Miller, Wolfson & Shaffer.*(46)

Heating and humidification

A laboratory study on mannequins has shown that commercially available HFNC devices vary in their ability to maintain the heat and relative humidity levels of inspired gases.(49) The study also found that certain CPAP devices provided similar (in some cases, better) heat and relative humidity levels compared to the HFNC device tested (see Table 4).(49)

These findings are supported by a clinical study measuring the temperature and relative humidity of gases delivered by HFNC (Vapotherm at 0-8 L/min) and CPAP, which found that HFNC gases were cooler (34.0 v 34.5⁰C p<0.01) but more humid (83% v 76% p<0.01).(50)

Table 4: Comparison of temperature and relative humidity of inspired gases of two high-flow nasal cannula devices

	1 & 4 L/min		8 L/min	
	Heat (°C)	Relative humidity	Heat (°C)	Relative humidity
Vapotherm	34.0	99	34.3	81.2
Optiflow junior	33.0	96	36.3	88.8

Source: Roberts, CT The effects of non-invasive respiratory support on oropharyngeal temperature and humidity: a neonatal manikin study.(49)

High-flow nasal cannula settings

There are no agreed standards for HFNC settings. Hence, the decisions regarding what flow rate to start, how and when to adjust flow, and what maximum flow rate to allow, remain areas of uncertainty.(43,44) The evidence on starting flow rates is complicated by the fact that some authorities advocate a flow rate per minute (L/min)(51), whilst others suggest weight-based flow rates (L/kg/min).(52) Schibler et al. suggest that the HFNC flow rate should ideally match the patient’s maximal inspiratory flow rate, so that room air need not be entrained; they estimate this would be approximately 2L/Kg/min for infants, and suggest it as a starting rate.(5)

To the author’s knowledge, there are no evidence-based, standardised or widely accepted HFNC protocols for HFNC initiation and/or subsequent adjustment, either in neonates or in children. Few authors have committed to suggesting guidelines. Two examples of those who have are (i) Duke et al., who suggest a flow-rate on a per kg basis, commencing at 2L/kg/min for the first 10 kg, adding 0.5L/kg/min for each kg thereafter (47), and (ii) Hutchings et al., who advocate for an age- and flow-rate-based protocol and provide guidance on four subsequent levels of adjustment.(51)

There is no uniformly agreed upon maximum HFNC flow rate, with review authors reporting anywhere between 8-60L/min as maximum rates used in their practice or in the studies they have reviewed.(1,2,6,43,44,53) Data collected from all UK PICU’s showed that 2605 (13%) of 19,967 admissions aged 0-15 years received HFNC, with the median flow rate across all units being 10 L/min (range 1-63 L/min).(54)

Magnitude of distending pressure

A concern with HFNC is the lack of any reliable, non-invasive way of measuring the magnitude of distending pressure applied to the patient's airway.(1,32,43,44,55) The pressure resulting from HFNC can be highly variable, even over short periods of time, and is dependent on a number of factors, including size of prongs relative to diameter of nares; patient weight; size of pharyngeal cavity; obstruction of nasal passages; and degree of mouth-leak.(32,44,45)

Studies (lab-bench, animal and in vivo) have attempted to measure the airway pressure generated by HFNC (44), but with conflicting results, as in the case of two studies in preterm babies: the one reported distending pressures of up to 8cm H₂O with as little as 1-2.5L/min(56), and the other, airway pressures of less than 6cm H₂O with 6L/min.(57) The lack of consensus may be due to the variety of methods employed to measure airway pressure, the variation in HFNC devices, flow rates and interfaces used in the studies, and the diversity of patients and settings studied.

Further non-invasive ventilation considerations

Interfaces

Despite the choice and type of NIV interface being critical to treatment success, there is little scientific evidence to provide guidance on which type of interface to use in children.(58,59) A wide variety of interfaces exist for NIV administration, including single or bi-nasal prongs, nasopharyngeal prongs, masks (nasal, oro-nasal, facial) and helmets; there are pros and cons associated with different interfaces (see Table 5). The selection of interface needs to be made on a case-by-case basis. It is important that a variety of shapes and sizes are available, especially in acute-care settings.(58)

Some interfaces are designed with intentional leak ('vented'), whereas others are intended for fully-sealed CPAP systems ('non-vented'). The choice will be determined by the type of CPAP device, the mode being used, the degree of respiratory distress, and the ability of the patient to tolerate a tight-fitting interface.(58)

Nasal prongs or nasal masks are most commonly used in neonatal patients, in part due to the lack of suitably-sized alternatives for this patient group; a wider range of interfaces are available for older children.(2,6) Nasal masks have smaller anatomical dead space, reduced risk of gastric distension, and improved tolerance of feeds compared to larger NIV interfaces, all of which are additional reasons for their suitability for neonatal patients.(58)

Interfaces that cover the mouth are tolerated better by older children and eliminate the problem of mouth-leak. However, they greatly compromise the ability to feed and interact.(58) Full face-masks cover the anterior surface of the face. They are more comfortable and less likely to cause local trauma, in that the seal-pressure is distributed over a larger surface area.(58)

Helmets are pressurised plastic bags that cover the whole head with a seal at the neck and points of gas entry (top) and exit (bottom) which allow gas flow; these can be used for CPAP and B_LCPAP.(58) The problems of seal-pressure are greatly reduced, and much higher CPAP pressure can be applied, but there are concerns about several aspects of this, including CO₂ rebreathing; interference with feeding; inability to place in supine position; and increased level of noise relative to standard CPAP.(58)

Table 5: Advantages and disadvantages of different interfaces for non-invasive ventilation in the acute setting

Type	Advantages	Disadvantages
Nasal	<ul style="list-style-type: none"> • Easy fitting • Allows coughing, eating, talking, use of a pacifier • No risk of aspiration • Low risk of claustrophobia • Less gastric distension • Low risk of asphyxia in case of ventilator malfunction 	<ul style="list-style-type: none"> • Mouth leaks • Not indicated if mouth breathing • Not indicated if nasal obstruction • Skin pressure ulcers
Nasal prongs	<ul style="list-style-type: none"> • Minimal contact interface • Comfortable 	<ul style="list-style-type: none"> • Not indicated if mouth breathing • Not indicated if nasal obstruction
Oro-nasal mask	<ul style="list-style-type: none"> • Improved gas exchange • Improved minute ventilation • No mouth leaks 	<ul style="list-style-type: none"> • Risk of aspiration • Claustrophobia • Gastric distension • Limit eating, talking
Full face	<ul style="list-style-type: none"> • Less pressure ulcers • Comfortable 	<ul style="list-style-type: none"> • Gastric distension • Claustrophobia • Higher dead space • Risk of aspiration
Helmet	<ul style="list-style-type: none"> • Allows eating, coughing, talking, pacifier • No pressure ulcers • Less resistance to flow, better tolerance to high pressure • More comfortable 	<ul style="list-style-type: none"> • Higher dead space • Ventilator adaptation • Difficult humidification • Claustrophobia, noise

Source: Mortamet G, *Interfaces for noninvasive ventilation in the acute setting in children.*(58)

Synchronisation

Synchronisation is not an issue for traditional single level CPAP or for HFNC, but it becomes an important consideration for B_iCPAP modes. The method used for synchronisation depends on the B_iCPAP device being used, but it usually involves pressure or flow sensors. Synchronisation is relatively easily accomplished in adults and older children because tight-fitting masks with little or no leak are feasible and these patients generate sizeable triggers.(4)

Synchronisation is problematic in small infants, particularly in premature neonates, as they are unable to generate adequate flow or pressure signals. In patients where masks do not fit well, the resulting leaks can cause problems with synchronisation. The seal can be further compromised by struggling uncomfortable patients, the presence of nasogastric tubes and/or craniofacial abnormalities.(59)

A variety of techniques have been adopted to improve neonatal synchronisation, including external respiratory inductance plethysmography(1,60) and sensitive in-line breath detectors (61), but these remain experimental. As yet no ideal device has been found for use in the neonatal settings.(1,2,6)

Neurally-adjusted ventilatory assistance (NAVA) is a promising new synchronisation technique which uses electromyography (EMG) signals from diaphragmatic muscles to allow adaptation to the phase of respiration and degree of work of breathing.(1) The NAVA EMG electrodes need to be placed in the oesophagus via a specially designed nasogastric catheter.(1)

Sedation

Patients with difficulty breathing are often anxious and distressed. NIV can add to the anxiety by covering the nose, mouth or face with NIV interfaces, which may need to be tightly applied. Small children are particularly likely to have increased upset and struggling associated with NIV, and this may interfere with respiratory support. There is no agreement on the need for sedation during NIV(62). There are, however, concerns that any form of sedation may adversely affect the patient's ability to self-ventilate.(53,62) Longrois et al. describe the use of a variety of drugs, including midazolam, dexmedetomidine, propofol and remifentanyl. They caution against use of benzodiazepine medication and suggest use of ketamine or dexmedetomidine.(62) Schibler et al. strongly advocate for dexmedetomidine

but acknowledge the limitation that this drug is not currently available outside of ICU settings.(53)

Adverse effects of CPAP and HFNC

The relative pros and cons of CPAP compared with HFNC use in children have been widely debated in the literature (1,2,6,32,43,44): the main features are summarised in Table 6.³ The two most commonly reported adverse effects of NIV in children relate, first, to the pressure-seal of the NIV interface and, secondly, to over-distention/air leak. These two factors are discussed in detail in this section, and a selection of these and other reported adverse effects are listed in Table 7.

Table 6: Comparative advantages and disadvantages of continuous airway pressure and high-flow nasal cannula

	CPAP	HFNC
Advantages	<ul style="list-style-type: none"> • In clinical use since 1970's • Well studied • Widely available • Staff familiarity 	<ul style="list-style-type: none"> • Simplicity of set-up • Ease of administration • Patient comfort • Ability to feed • Improved interaction • Reduced sedation requirement
Disadvantages	<ul style="list-style-type: none"> • Tight-seal required • Discomfort • Nasal trauma • Synchronisation needed for BiCPAP 	<ul style="list-style-type: none"> • Unpredictable airway pressure • Fewer studies/evidence • Devices less widely available • Staff unfamiliar

Pressure-seal related trauma

Perhaps the most widely reported adverse effects of NIV relate to nasal trauma, ranging from mucosal irritation to damage of the philtrum, permanent flaring of the nostrils, snubbing of the nose and necrosis of the *collumella nasi*.(1,31,32) Nasal trauma is linked to the type of NIV interface and the method used to secure the interface in place.(32,58,59) The tightness of the seal required for some CPAP devices can cause damage through direct pressure damage to the skin and underlying tissues. This damage may be compounded through the occlusive seal generated by some interfaces: the associated increased sweating and potential

³ Note that this table was created by Baljit Cheema for this dissertation.

maceration of the skin, alters the skin's tolerance to frictional forces and could potentially be a portal of entry for infection.(59,63,64)

In neonates, there is evidence of greater risk of nasal trauma in patients treated with CPAP compared with HFNC (see the section on clinical effectiveness of NIV in children). However, there are concerns that two of the largest studies, contributing most data to these findings, had excessively high rates of nasal trauma in their CPAP groups. Manley et al.(65) in a post-extubation study of preterm infants (<32 weeks GA) reported 53% and Yoder et al.(66) 17% nasal trauma in CPAP groups in their studies. It has been argued that this is in stark contrast to CPAP nasal trauma rates in other studies, which have been as low as 0.2%.(67)

Historically, there are reports of neonatal CPAP being associated with cranial vault deformities, cerebellar haemorrhages and resultant hydrocephalus, which are likely to be related to the relatively harsh-strapping techniques and interfaces that were made from less flexible materials.(32)

Over-distension and air leak

Another major category of NIV adverse effect is that of excessive airway pressure leading to over-distension of internal structures, with or without subsequent air leak. Pulmonary air leaks are thought to be further related to shear trauma from repeated expansion of collapsed areas of lung.

Air leaks and over-distension problems have been widely reported in the literature for both CPAP and HFNC. There is a pattern of more reports overall and a higher rate of air leaks, of different types associated with CPAP (see Table 7). This is understandable from a mechanical perspective as CPAP is more often a closed-system, whereas HFNC is intended to have a high-degree of leak. Nevertheless, as discussed earlier, HFNC may also generate unpredictably high airway pressures, especially if there is a blockage to expiratory flow. The greater cumulative number of CPAP-related air leak cases may be due in part to the fact that CPAP has been in clinical use for longer, especially as the earlier era involved use of higher CPAP pressures and with less-nuanced devices.

Table 7: Selection of adverse events reported with NIV use in children

Domain	Adverse event
Over-distention and/or air leak	<ul style="list-style-type: none"> • Pneumothorax* • Pulmonary interstitial emphysema(68–70) • Pneumatocele(71) • Pneumo-mediastinum(72,73) • Pulmonary vascular air embolism(74) • Pneumo-pericardium(73,75–77) • Pneumo-cephalus(78) • Pneumo-orbitis(77) • Bowel distension(79) • Bowel perforation(80) • Subcutaneous emphysema(72,73)
Head and neck	<ul style="list-style-type: none"> • Nasal trauma* • Skull deformity & intra-cerebellar haemorrhage(81) • Decreased CBF with helmet interface(82)
Infection	<ul style="list-style-type: none"> • <i>Ralstonia mannitolilytica</i>(83) • <i>Burkholderia cepacia</i>(84) • Gram-negative septicaemia(85)
Other	<ul style="list-style-type: none"> • Steam burn to nose with HFNC(86) • Delay to IPPV(87) • Interference with BVM resuscitation (88)

GIT, gastro-intestinal tract; CBF, cerebral blood flow; HFNC, high-flow nasal cannula; IPPV, invasive positive pressure ventilation; BVM, bag-valve-mask; *Widely reported in the literature.

Note: This list was compiled by non-systematic noting of adverse events reported in studies (or references) evaluated during the course of this literature review and is not exhaustive. References are given for rarer adverse events (<five reports identified).

Clinical Effectiveness of NIV in Children

Systematic review (with or without meta-analysis) is relied upon in this section, which reviews the evidence on clinical effectiveness of NIV. The focus is on NIV use in neonatal populations, due to the predominance of research on this group. There is additional review of NIV use in paediatric acute respiratory distress and HFNC clinical use in children.

Scope of clinical evidence reviewed

The literature on NIV in transport settings will not be reviewed here, as it is the subject of the systematic review in the following chapter. Outside of adult settings, most NIV research has been conducted in the NICU environment. Unfortunately, research evidence of the same extent does not exist for other paediatric patient groups: PICU, paediatric wards and emergency areas.(2)

It is beyond the scope of this literature review to conduct a series of systematic reviews of the literature on NIV clinical effectiveness in all neonatal and paediatric settings. Individual study data will not be discussed, but instead systematic review data (with or without meta-analysis) will be used to address important NIV outcomes, and unless, otherwise stated, quality-of-evidence classification will be made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.(89)

In keeping with the greater volume and maturity of NICU NIV research compared to other domains, this section focuses on relevant data from a selection of recent systematic reviews (with meta-analyses) on clinical effectiveness of NIV in NICU settings: Subramaniam et al.(41); Ferguson et al.(90); Wilkinson et al.(45); Lemyre et al.(91) and Kotecha et al.(67). Evidence from the paediatric realm will be limited to summarising four recent reviews, one of which evaluates literature on NIV in Paediatric Acute Respiratory Distress Syndrome (PARDS)(92), and the others of which review the literature on HFNC in children: Beggs et al(93); Mayfield et al.(94) and Mikalsen et al.(95)

Neonatal NIV

Due to the particular vulnerability of new-born and preterm infant lungs to the damaging effects of IPPV, NIV has been actively studied in this patient group for decades. Systematic review (SR) and meta-analysis (MA) data presents a relatively well-defined picture of potential benefits and harms associated with NIV in this group.

CPAP compared with oxygen therapy

There is very low-quality evidence that CPAP has fewer treatment failures when compared with supportive care (including oxygen therapy)(41) (see Table 8). In comparison with head-box oxygen, there is low quality evidence that CPAP reduces the incidence of extubation failure within seven days (NNTB 6), but there was no reduction in the number of infants requiring reintubation within seven days.(90) The study authors postulate that this is because many head-box oxygen failures were successfully managed with CPAP.

There is no evidence that CPAP, compared with supportive care (including oxygen therapy), leads to reduced incidence of pulmonary air leaks, CLD, death or the combined outcome of death or CLD in preterm infants.(41)

The evidence comparing CPAP with assisted ventilation is detailed in Table 8. There is moderate level evidence that CPAP compared with assisted ventilation reduces the number of preterm infants requiring IPPV by approximately half. This evidence is based on data from two studies, including a total of 1042 infants. Both studies were well-conducted multi-centre RCT studies: one was conducted across 27 centres in Canada and the US over a six-year period (96), and the other was enrolled across centres in Australasia, Europe and the US over seven years.(42)

Continuous positive airways pressure, compared with assisted ventilation, was found to reduce CLD at 28 weeks GA in one study (610 infants) that reported no sustained reduction beyond that age.(42) However, meta-analysis of three trials (2150) found moderate-level evidence of reduction in the incidence of CLD at 36 weeks GA (NNTB 25).(41)

There is no difference in the outcome of death between infants randomised to CPAP or assisted ventilation; however, there is a reduction in the combined outcome of death or CLD: RR 0.89 (95% CI 0.81-0.97); 2358 infants, three studies, NNTB 20.

With regard to pulmonary air leaks, there is moderate level evidence that use of higher CPAP pressure of 8cm H₂O compared with 5cm H₂O was associated with a three-fold increase in risk of pneumothorax.(41) This result was heavily influenced by one study in which infants randomised to CPAP were commenced on starting level of 8cm H₂O; there was a 9.1% incidence of pneumothorax in the CPAP group, compared with 3.0% in IPPV group (NNTB 17).(42) The study authors argue in favour of higher CPAP pressures due to benefits in terms of improved FRC, lung compliance and oxygenation, with no discernible increase in any other adverse outcomes apart from pulmonary air leak.

Table 8: Clinical effectiveness of continuous positive airway pressure in neonates

Comparison	Outcome	Study	No. of Participants (No. of Studies)	Relative effect (95% CI)	NNT	Quality (GRADE)
Failed treatment						
CPAP v supportive	Failed treatment	Subramaniam	765 (4)	0.66 (0.45-0.98)	-	Very low
CPAP v head-box oxygen	Extubation failure	Ferguson	667 (8)	0.59 (0.48-0.72)	6	Low
	Reintubation <7d	Ferguson	667 (8)	0.83 (0.66-1.04)	-	Low
CPAP v IPPV	Assisted ventilation	Subramaniam	1042 (2)	0.49 (0.45-0.54)	-	Moderate
Chronic lung disease						
CPAP v supportive	O ₂ at 28wks GA	Subramaniam	535 (3)	1.02 (0.77-1.36)	-	Moderate
CPAP v supportive	O ₂ at 36wks GA	Subramaniam	683 (3)	0.79 (0.5-1.24)	-	Moderate
CPAP v IPPV	O ₂ at 28wks GA	Subramaniam	610 (1)	0.81 (0.70-0.94)	-	-
CPAP v IPPV	O ₂ at 36wks GA	Subramaniam	2150 (3)	0.89 (0.80-0.99)	25	Moderate
Mortality						
CPAP v supportive	Mortality to latest FU	Subramaniam	765 (4)	1.04 (0.56-1.93)	-	Moderate
CPAP v IPPV	Mortality at anytime	Subramaniam	2358 (3)	0.82 (0.66-1.03)	-	Moderate
CPAP v supportive	Mortality to latest FU	Subramaniam	256 (1)	0.69 (0.40-1.19)	-	Moderate
CPAP v IPPV	Mortality at anytime	Subramaniam	2358 (3)	0.89 (0.81-0.97)	20	Moderate
Pulmonary air leak						
CPAP v supportive	Pulmonary air leaks	Subramaniam	586 (3)	0.75 (0.35-1.61)	-	Moderate
CPAP 5-8cm v IPPV	Pulmonary air leaks	Subramaniam	2357 (3)	1.24 (0.91-1.69)	-	Moderate
CPAP 5 cm v IPPV	Pulmonary air leaks	Subramaniam	1747 (2)	0.96 (0.67-1.37)	-	Moderate
CPAP 8cm v IPPV	Pulmonary air leaks	Subramaniam	610 (1)	3.07 (1.47-6.40)	-	Moderate

CI, confidence interval; NNT, number needed to treat; CPAP, continuous positive airway pressure, O₂, oxygen; GA, gestational age; IPPV, invasive positive pressure ventilation; FU, follow up. See Appendix D for details of systematic review and meta-analysis studies used in this table. References: Subramaniam et al.(41); Ferguson et al.(90)

CPAP compared with assisted ventilation

NIPPV compared with CPAP

As previously discussed, there are many variants of bi-level NIPPV, including Bi-PAP, NIPPV and SNIPPV, with a range of devices, interfaces and settings for each of these modes. With

increasing recognition of potential difference in clinical effectiveness between different types of NIPPV, more recent reviews have separated out the NIPPV variants and compared them CPAP (see Table 9).

Table 9: Clinical effectiveness of non-invasive positive airway pressure in neonates

Comparison	Outcome	Study	No of participants (No. of studies)	Relative effect (95% CI)	NNT	Quality (GRADE)
Failed treatment						
NIPPV v head-box	Failed extubation	Ferguson	90 (1)	0.25 (0.12-0.51)	3	-
Any mode NIPPV or BiPAP v CPAP	Extubation failure	Ferguson	1368 (9)	0.70 (0.60-0.81)	8	Low
	Reintubation <7days	Ferguson	1368 (9)	0.74 (0.64-0.85)	10	Low
	Respiratory failure	Lemyre	876 (9)	0.62 (0.47-0.82)	-	Moderate
	Intubation	Lemyre	766 (8)	0.79 (0.64-0.97)		Moderate
Non-synchronised NIPPV v CPAP	Extubation failure	Ferguson	251 (3)	0.64 (0.44-0.95)	8	ND
Synchronised NIPPV v CPAP	Extubation failure	Ferguson	272 (5)	0.25 (0.15-0.41)	4	ND
Chronic lung disease						
NIPPV v CPAP	O ₂ at 36wks GA	Lemyre	899 (9)	0.78 (0.58-1.06)	-	Moderate
Mortality						
NIPPV v CPAP	Mortality during study period	Lemyre	876 (9)	0.77 (0.51-1.17)	-	Low
Pulmonary air leak						
NIPPV v CPAP	Pneumothorax	Lemyre	876 (9)	0.69 (0.35-1.34)	-	Moderate

CI, confidence interval; NNT, number needed to treat; NIPPV, non-invasive positive pressure ventilation; CPAP, continuous positive airway pressure, ND, not documented; O₂, oxygen; GA, gestational age; IPPV, invasive positive pressure ventilation; FU, follow up. See Appendix D for details of systematic review and meta-analysis studies used in this table. References: Ferguson et al.(90); Lemyre et al.(91)

Two recent studies have reviewed and meta-analysed data on this topic: Lemyre et al.(91) included 10 studies evaluating early NIPPV versus early CPAP in preterm infants, while Ferguson et al.(90) included 10 NIPPV studies in their review of interventions to improve extubation success. Interestingly, the papers they reviewed had almost no overlap, with only one study in common, yet they have remarkably similar findings. Both reviews found NIPPV to be superior to CPAP, with a 30-38% reduction in respiratory failure and 21-26% reduction in intubation rates, and with neither of them finding any difference in rates of CLD, death or pneumothorax.(90,91)

When compared with CPAP, S-NIPPV appears to be twice as effective as NIPPV at preventing extubation failure, with one extubation failure prevented for every four infants versus treated with S-NIPPV versus one for every 8 infants treated with NIPPV when compared to CPAP.

HFNC compared with CPAP or NIPPV

Wilkinson et al. published a 2016 update of their review of HFNC for respiratory support for preterm infants (<37 weeks GA) in the Cochrane Database of Systematic Reviews.(45) They compared HFNC with CPAP and NIPPV in two preterm patient groups: (1) infants receiving NIV as primary respiratory support without a period of prior IPPV (439 infants, four studies), and (2) infants requiring respiratory support following a period of IPPV (934 infants, six studies). Ferguson et al.(90) also meta-analysed data from six studies (all of which were included in the Wilkinson study). However, they analysed the studies purely from the point of view of extubation failure. Thus, they extracted data differently from the Cochrane review and hence their findings are listed as well in Table 10.

The findings of these reviews indicate that there is no difference between HFNC and CPAP for treatment failure, reintubation, CLD or death. The only significant finding reported in two reviews (45,67) is that reduced nasal trauma has been found in patients treated with HFNC compared with CPAP. However, there is reason to be cautious in the interpretation of this finding, as both reviews were heavily influenced by data from two trials (65,66) that both had unusually high rates of nasal trauma in the CPAP and HFNC groups: 19% HFNC and 53% CPAP (65), and 10% HFNC and 17% CPAP (66). These rates seem to be incongruous when compared with other studies reporting nasal trauma rates of the order of 0.2-3% (97,98)

Wilkinson et al.(45) identified one study (99) reporting on HFNC versus NIPPV, and this found no difference in rates of treatment failure, CLD or death.

Table 10: Clinical effectiveness of high flow nasal cannula therapy in neonates

Comparison	Outcome	Study	No. of participants (No. of studies)	Relative effect (95% CI)	Quality (GRADE)
Failed treatment					
HFNC v CPAP	1 ^o support: Failed treatment <7days	Wilkinson	439 (4)	1.30 (0.73-2.34)	10 ND
	2 ^o support: Failed extubation	Wilkinson	786 (5)	1.21 (0.95-1.55)	38 ND
	2 ^o support: Reintubation <7days	Wilkinson	934 (6)	0.91 (0.68-1.20)	22 ND
	Respiratory failure	Ferguson	658 (3)	1.11 (0.84-1.47)	55 Very low
	Reintubation <7days	Ferguson	698 (4)	0.94 (0.68-1.31)	64 Very low
HFNC v NIPPV	Failed treatment <7days	Wilkinson	76 (1)	'No difference'	- ND
Chronic Lung Disease					
HFNC v CPAP	2 ^o support: O ₂ at 28 days if born >32wks GA or O ₂ at 36wks if born <32wks GA	Wilkinson	893 (5)	0.96 (0.78-1.18)	0 ND
HFNC v NIPPV	O ₂ at 28 days if born >32wks GA or O ₂ at 36wks if born <32wks GA	Wilkinson	76 (1)	'No difference'	- ND
Mortality					
HFNC v CPAP	Death before discharge	Wilkinson	896 (5)	0.77 (0.43-1.36)	0 ND
HFNC v NIPPV	Death before discharge	Wilkinson	76 (1)	'No difference'	- ND
Nasal trauma					
HFNC v CPAP	Nasal trauma	Wilkinson	645 (4)§	0.64 (0.51-0.79)	44 ND
	Nasal trauma (undefined)	Kotecha	857 (5)§	0.13 (0.02-0.69)	41 ND

CI, confidence interval; HFNC, high-flow nasal cannula; CPAP, continuous positive airway; 1^o, primary; 2^o, secondary; ND, not documented; NIPPV, non-invasive positive pressure ventilation pressure; O₂, oxygen; GA, gestational age; IPPV, invasive positive pressure ventilation; FU, follow up. See Appendix D for details of systematic review and meta-analysis studies used in this table. References: Wilkinson et al.(45); Ferguson et al.(90); Kotecha et al.(67)

NIV for Paediatric Acute Respiratory Distress Syndrome

The Paediatric Acute Lung Injury Consensus Conference (PALICC) published recommendations in 2015 on the use of NIV for PARDS based on a review of the literature.(92) Due to a lack of RCT evidence, they included a broad range of study types and used the Research And Development University of California, Los Angeles (RAND/UCLA) Appropriateness Methodology(100) to reach consensus. This is a tool for areas lacking RCT evidence, which aims to combine available scientific evidence with expert judgement to help reach decisions on the appropriateness of using procedures for different patient groups.

The study concluded that there was insufficient evidence on HFNC to permit the making of recommendations. For CPAP and CPAP variants, 13 studies were included, of which 12 were descriptive studies and one was a RCT.(92) The included RCT randomised 50 children admitted to PICU with acute respiratory failure, to standard care or bi-level NIV and found significant reduction in intubation in the NIV group (28% v 60%; $p=0.045$) with no difference in length of ICU/hospital stay; they did not report mortality or air leak data.(101)

The PALICC recommendations most relevant to this study are summarised in Table 11 overleaf.

It has to be remembered that these recommendations are based on low-level evidence and that even when combined with expert judgment, they are still not equivalent to RCT data. Outside of the NICU setting, this lack of RCT evidence of clinical effectiveness of NIV seriously hinders the ability to make strong recommendations about how, where, when and in whom NIV should be used. Unfortunately, this has not held back the surge of interest and widespread use of NIV in non-NICU settings.

Table 11: Selection of Paediatric Acute Lung Injury Consensus Conference Recommendations

Conclusion from evidence	Recommendation	Level of agreement
There is relatively little published data to support the routine use of NPPV for the treatment of PARDS.	7.1.1 We recommend that NPPV be considered early in disease in children at risk for PARDS to improve gas exchange, decrease work of breathing, and potentially avoid complications of invasive ventilation.	Weak agreement (88% agreement)
The high level of NPPV failure in moderate and severe PARDS suggests that NPPV is not indicated in those populations.	7.4.2 NPPV is not recommended for children with severe disease.	Strong agreement
NPPV should only be performed for children with PARDS in an acute-care setting with continuous monitoring and where invasive ventilation is also available.	7.2.1 We recommend that, although non-invasive, NPPV should be delivered in a setting with trained experienced staff and where close monitoring is available to rapidly identify and treat deterioration.	Strong agreement
The efficacy of NPPV is associated with a good patient-ventilator interface. Appropriately fitting masks will improve tolerance of NPPV therapy. Facial or oronasal masks provide superior support to nasal and helmet interfaces in children with PARDS due to reduced air leaks and increased patient-ventilator synchrony	7.3.2 We recommend the use of an oronasal or full facial mask to provide the most efficient patient-ventilator synchronization for children with PARDS.	Weak agreement (84% agreement)
In PARDS, bi-level ventilation that provides an increased level of support during inspiration will provide a superior level of support than continuous positive pressure alone.	7.3.6 To reduce inspiratory muscle effort and improve oxygenation, we recommend non-invasive pressure support ventilation combined with positive end-expiratory pressure in patients with PARDS. Continuous positive airway pressure alone may be suitable for those children who are unable to attain patient-ventilator synchrony or when using	Weak agreement (92% agreement)

NPPV, non-invasive positive pressure ventilation; PARDS, paediatric acute respiratory distress syndrome. Note: The numbering of recommendations has been kept as per the Paediatric Acute Lung Injury Consensus Conference report.(108)

HFNC in children

Two Cochrane systematic reviews have reported on the evidence for the clinical effectiveness of HFNC in children.(93,94) Beggs et al.(93) evaluated research on infants with bronchiolitis and included only one pilot study (51) in which 19 patients were randomised to HFNC or head-box oxygen. The primary outcomes of the study were oxygen saturations levels at different time-points. The study found significantly higher median oxygen saturation levels in the HFNC group at eight and 12 hours but not at 24 hours; no child experienced adverse effects, none required intubation on CPAP and there was no reported difference in duration of oxygen therapy or length of hospital stay. The second Cochrane review, of HFNC for respiratory support in children (excluding bronchiolitis), found no studies meeting their inclusion criteria.(94)

In a more recent review of HFNC in non-neonatal paediatric settings, 26 studies were included: five interventional studies (4 RCT) and 21 observational studies (seven studies with control group; 14 studies without control group). Thirteen studies focused only on children with bronchiolitis, of which six were conducted in PICU, five in paediatric wards and two in emergency departments.(95) This review did not define outcome measures, nor did it attempt to assess the risk of bias of included studies or evaluate the strength of evidence for conclusions. There was low-level evidence of potentially reduced intubation rates, short-term improvement in oxygen saturation levels, reduced respiratory rate and improved blood gases and decreased admission to PICU. Reports of adverse events with HFNC were few: two studies had 'four serious cases of pneumothorax', and three studies suggested abdominal distension in children on HFNC. A difficulty in interpreting the information in this review is that the authors frequently did not report what form of therapy the comparison groups received and only partially reported actual data from the studies.

The Setting

The critical-care transport environment necessitates some paradoxical requirements from equipment, staff and patients. For example, items must be mobile yet safely securable; equipment should be multifunctional, yet small and lightweight; the few staff must be multi-skilled to high levels; patients are critically ill enough to need transfer but not so unstable that they deteriorate en route.(102) To transfer critically ill neonates and children presents its own special challenges. Those relevant to NIV use during transport will be discussed in this section.

Figure 6: List of recommendations for transfer of critically ill patients

- *Critically ill patients should be transferred by a specialised retrieval team.*
- *Intensive care should not be interrupted by transportation of the patient.*
- *Specialised retrieval teams should receive transfer training.*
- *Specific training programmes should be developed.*
- *Specialised retrieval teams should be staffed by a physician, preferably an intensivist and an ICU nurse.*
- *The accompanying physician makes the final decision whether the patient is transferrable and which treatment is given during the transport.*
- *Experience and training are more important than speed.*
- *Transfer organisations should have a quality management system.*
- *Incident reporting should be standardised and mandatory.*
- *Equipment used should conform with both ICU and transfer standards.*
- *Adults can learn from children (in the organisation of transport).*

Source: Droogh et al. Transferring the critically ill patient: are we there yet? (25)

Centralisation of critical-care services

A 1993 British report found that only 51% of critically ill children in the UK were cared for in dedicated Paediatric Intensive Care Units (PICUs), with the remainder being cared for in a variety of settings, including paediatric wards and adult ICUs.(103) During the 1990s this situation was increasingly recognised as unacceptable as there was mounting evidence of improved outcomes for critically ill children managed in designated PICUs.(104,105)

Subsequently, there has been a major reconfiguration of critical-care services for children and neonates in developed countries over the past 25 years, which has necessitated increased numbers of sick children being transported between health facilities.(25,104,106,107). In tandem with this, there has been an evolution of specialised retrieval teams to transport children to and from these units.(104,108) The British Paediatric

Intensive Care Audit Network (PICANet) collects data from all 34 PICUs in Great Britain, as well as from six dedicated paediatric retrieval services. Their report for the three-year period 2013-2015 included 58,951 PICU admissions; during this time, 15,844 transports were done by RTs, of which 13,278 (83.8%) were non-elective admissions and 61.5% took less than one hour.(54)

Retrieval teams

Retrieval Teams (RTs) have many different formats (109,110) and the literature suggests significantly better outcomes with specialised paediatric RT transport compared with non-specialised transport.

Specialised versus non-specialised transport team

Amongst 1085 transports to Philadelphia Children's Hospital, 1021 (94%) were transferred by specialist team and 64 (6%) by non-specialist RT. Non-specialist versus specialist transports had a higher incidence of adverse events 51% v 1.5% and mortality 23% v 9%. Following adjustment for severity of illness, the only factor associated with increased risk of adverse events (RR: 53.4 [95% CI: 36.1-62.8]) and mortality (RR:2.2 [95% CI: 1.13-3.80]) was non-specialist team transfer. However, numbers in non-specialist transport group were small and contained significantly more cardiac and neurological cases compared to specialist transfers.(111)

In a second study of UK PICU transfer data, complete data was available on the type of retrieval team for 16875 (96%) of 17,649 transfers from other hospitals. Of these, 13,729 (81%) were done by specialist RTs and 3146 (19%) by non-specialists RTs. Multivariate analysis, after adjustment for factors including age, sex and paediatric index of mortality score, showed reduced mortality (0.58, 0.39-0.87) in the specialist RT transfer group compared to non-specialist transfers.(105)

Staffing composition

Staff skill-mix varies greatly in pre-hospital settings, with one study identifying 25 different team compositions.(108) The US pattern of staffing seems to rely on a nurse-plus-technician team format. One study reported that all but one of 335 neonatal RTs surveyed utilised a nurse in the RT and that the most common team composition was nurse-respiratory therapist (44.3%) amongst dedicated RTs.(112) The Australasian and UK models use nurse-physician combinations, with the physicians most commonly being senior trainees.(104,109) European

RTs are more commonly staffed by physician-paramedic teams with specialist physicians rather than trainees.(9)

Transport technical limitations for non-invasive ventilation

The transport situation is distinct from facility-based healthcare because of significant differences such as environmental constraints, staff numbers, skill-mix and nature of the work.(9,25,102) Some of the most relevant technical limitations relating to NIV in the transport setting will be discussed next.

Medical gas supply

Non-invasive ventilation is mechanically reliant on the primary gas supply and therefore consumes a high volume of medical gas. Neither piped medical gases nor a concentration of oxygen from the atmosphere are feasible in the transport setting. This means reliance on compressed gases in cylinders: oxygen cylinders are widely available, but compressed air is less widely available in the transport setting. Administration of high FiO₂ is potentially harmful to patients, especially neonates, and must therefore be titrated to the lowest necessary concentration by blending with air.(32,53,113) Medical air is produced by compression from the atmosphere, and some of the newer ventilators and NIV devices are able to entrain room air to allow blending of oxygen with air.(114,115)

Power supply

Almost all critical-care transport equipment is power-dependent, and since battery power is essential, ideally all equipment should have several hours of battery-life.(25,102) Whilst transport ventilators have batteries, many standalone NIV devices, such as HFNC machines do not have battery-power capability. Power supply and recharging options are very limited in helicopter transfers, which needs to be a consideration for all forms of assisted ventilation.(116,117)

Heating and humidification of inspired gases during transport

Standard heating elements rapidly deplete battery power, and so heating and humidification of inspired gases can be problematic when ventilation devices are not plugged in. One commercially available exception is the Neo-Pod 'T' heating device, coupled with a Lavabed humidifier (Westmed Inc, Tucson Az, US) which is specifically designed for the transport environment.(118)

Technical adverse events

Equipment- and technology-related adverse events are amongst the commonest types of problems encountered in the transport setting (see Table 12).

Table 12: Adverse technical events during paediatric inter-facility transport

System		Number of events
Gas supply	leakages	3
	dysfunctional gas tube connectors	5
	defective connectors of 2 -litre tanks	3
	unintentional use of 2-litre tanks	3
Electrical system	defective dynamo	2
	blown fuses	4
Mobile Intensive Care Unit ambulance	starting problems	1
	dysfunctional loading bridge	
	dysfunctional exterior lights	2
	collision	1
	dysfunctional heating/air conditioning	2
	minor defects on doors	4
	defective suspension	1
Equipment	dysfunctional monitor	1
	dysfunctional perfusion pump	1
	defective battery ventilator	1
	defective battery defibrillator	1
Trolley	dysfunctional brake system (blown fuses)	6
	damaged bolting system trolley	4
	collision damage on trolley or equipment	7

Source: Droogh et al. Inter-hospital transport of critically ill patients: expect surprises. (26)

Non-invasive ventilation in transport setting

Rationale

Non-invasive ventilation has become increasingly popular in critical care and emergency settings over the past 15-20 years, but its availability in the pre-hospital setting has been slower to evolve. If NIV is unavailable in transport, then patients on NIV who need to be transported between facilities will have to be intubated and placed on IPPV just for transport. There is growing interest in filling this gap, and it has been recognised as a priority by several EMS bodies internationally.(9)

Effectiveness of non-invasive ventilation in transport of adult patients

As part of a process to decide whether to introduce NIV in the pre-hospital setting, the UK National Institute of Health Research (NIHR) recently undertook an independent Health Technology Assessment (HTA). The HTA process included a comprehensive systematic review, with independent patient data (IPD) meta-analysis, of clinical effectiveness and cost-effectiveness of NIV for ARF in *adult* patients in the pre-hospital setting.(9)

The review included 10 studies (eight RCT; two QRCT; six CPAP; four BiPAP; sample size 23-207 patients) and with IPD for 650 patients from seven trials. The study found that when compared with standard pre-hospital care, CPAP (but not BiPAP) reduced the risk of mortality (OR 0.41; 95% credible interval (CrI)0.20-0.77) and intubation rate (OR 0.32; 95% CrI 0.17-0.62). It was estimated that CPAP was both more effective and more expensive than standard care, but that overall cost-effectiveness was uncertain.(9)

Issues regarding non-invasive research in pre-hospital setting

Caution needs to be exercised in the interpretation of NIV research from non-transport settings as the environment, staffing, equipment and patient presentations are very different in transport compared with health facilities; so the research cannot be directly

Table 13: Factors to consider when comparing pre-hospital NIV research

Team	<ul style="list-style-type: none">• Specialised v non-specialised team• Staff composition
Transport	<ul style="list-style-type: none">• Mode• Distance• Duration
NIV	<ul style="list-style-type: none">• Type of NIV• NIV generating device used• Type of interface• Heating & humidification of gases• Initiated by referring facility or by RT
Indication	<ul style="list-style-type: none">• Escalation of level of care• Step down to lower level of care• Transport for procedure or investigation• From home or only between facilities• Chronic NIV patient

NIV, non-invasive ventilation; RT, retrieval team

translated into the pre-hospital setting.(9) It is heartening to see increasing research reports of NIV being used (primarily in adult patients) in Europe, Australasia and the US. Some of the variables that might affect clinical outcomes of pre-hospital NIV research are summarised in Table 13.⁴

⁴ Note: this table was created by Baljit Cheema for this dissertation.

CHAPTER 3:

RESEARCH QUESTION

AND STUDY OBJECTIVES

Research Question

The question this study aims to answer is: In children aged from 0 days to 18 years, who are hospitalised with acute respiratory distress and require inter-facility transport, is non-invasive ventilation, effective and safe during transport?

Definition of terms

For the purposes of this study the following definitions were used:⁵

- **Acute respiratory distress** includes evidence of (but not limited to) one or more of the following criteria preceding transport, as defined by the study authors:
 - abnormal respiratory rate (RR);
 - increased work of breathing (WOB);
 - low oxygen saturation (SaO₂); and
 - blood gas results (arterial, capillary or venous) suggestive of respiratory compromise.
- **Inter-facility transport (IFT)** involves movement of patients between healthcare facilities by trained pre-hospital providers.
- **Standard oxygen therapy (SOT)** refers to any of the following modes of oxygen delivery:
 - low-flow oxygen (<2 l/min) delivered by nasal cannulae or prongs;
 - oxygen at any flow rate delivered by facemask: simple, partial rebreathing or non-rebreathing; and
 - oxygen delivered by other non-invasive means such as headbox, tent, hood or cot O₂.
- **Invasive positive pressure ventilation (IPPV)** is any form of traditional mechanical ventilation where positive pressure is administered directly to the lungs through an endotracheal tube (ETT), supraglottic airway (SGA) device or tracheostomy tube.
- **Non-invasive ventilation (NIV)** is any modality of assisted ventilation for spontaneously breathing patients that does not require the presence of an indwelling ETT, SGA device or tracheostomy tube. Studies of external negative pressure devices will be excluded. NIV will be considered in two separate groups: continuous positive airway pressure (CPAP) and high-flow nasal cannula (HFNC) therapy. (For details of the definitions used in this study, see Table 2.)

⁵ However, when describing findings from specific studies, the terms and definitions used by the authors will have to be relied on.

Study Objectives

The objective of this study was to evaluate the research evidence regarding the effectiveness and safety of NIV for children with acute respiratory distress requiring inter-facility transfer.

Outcome measures

The primary outcome measures related to the safety of NIV in preventing escalation of respiratory support and lack of adverse events during transport. Secondary outcome measures pertained to relative effectiveness in terms of improvement of respiratory and ventilatory parameters and any effect on mortality following transportation.

Primary outcomes

1. The primary outcomes measures consisted of the following safety indicators :
 - 1.1. Intubation rate during transport or soon after transfer.
 - 1.2. Escalation to any form of more invasive ventilation during or soon after transfer.⁶
 - 1.3. Adverse events during the transport phase, including the following:
 - apnoea
 - desaturation
 - bradycardia
 - bag-mask ventilation
 - cardio-pulmonary resuscitation.

Secondary outcomes

2. The secondary outcome measures consisted of effectiveness indicators which were taken as markers of the impact of NIV during transport, on clinical and ventilatory parameters, during or after transport. These included the following:
 - 2.1. heart rate (HR)
 - 2.2. respiratory rate (RR)
 - 2.3. work of breathing (WOB)
 - 2.4. measures of oxygen saturation (SaO₂)
 - 2.5. fractional inspired oxygen (FiO₂)
 - 2.6. measures of blood carbon dioxide (CO₂)
 - 2.7. mortality.

⁶ For CPAP escalation to more invasive ventilation is taken to mean escalation to IPPV. For HFNC escalation to more invasive ventilation is taken to mean escalation to CPAP or IPPV.

CHAPTER 4: STUDY METHODOLOGY

Protocol and Registration

The protocol for this study was submitted to the University of Cape Town Human Research Ethics Committee in October 2016. The protocol reference number is FHS030-2016.

Study Type

This study was a systematised review of the literature⁷. The rigorous principles of Cochrane collaboration systematic reviewing methodology(11,119) were employed, but with limitations on the extent of the search.

Eligibility Criteria

Inclusion criteria

Studies

Randomised or quasi-randomised controlled trials (RCT/QRCT) comparing NIV to standard respiratory interventions in pre-hospital settings were the preferred level of evidence to answer the research question. In the absence of RCT/QRCT evidence being identified in the search, the study protocol permitted inclusion of non-randomised studies of interventions (NRSI). In the absence of NRSI (or less than 10 such studies in total), case-series studies would be included.

Settings

Studies based partly or wholly in the inter-facility transport (IFT) setting were included.

Participants

Children with acute respiratory conditions aged from birth to 18 years were included. This includes new-born infants, whether born at full term or prematurely.

Interventions

The types and sub-types of NIV as defined in Table 2 (see Chapter 2: Literature Review) were:

- a) continuous positive airway pressure (CPAP) and CPAP variants; and
- b) high-flow nasal cannula (HFNC) oxygen therapy.

⁷ Based on the classification of reviews by Grant & Booth(12)

Outcome measures

In order to be eligible for inclusion, the studies needed to report on at least one of the primary outcome measures. If a study reported only secondary outcomes but no primary outcome measures, it was not considered eligible for inclusion.

Primary outcomes

- Primary efficacy and safety indicators were:
 - Intubation rate during transport or soon after transfer.
 - Escalation to any form of invasive ventilation during or soon after transfer.
 - Adverse events during the transport phase, included the following:
 - apnoea
 - desaturation
 - bradycardia
 - bag-mask ventilation
 - cardio-pulmonary resuscitation.

Secondary outcomes

- Secondary effectiveness and safety indicators were markers of the impact of NIV during transport, on clinical and ventilatory parameters, during or after transport. These included the following:
 - heart rate (HR)
 - respiratory rate (RR)
 - work of breathing (WOB)
 - measures of oxygen saturation (SaO₂)
 - fractional inspired oxygen (FiO₂)
 - measures of blood carbon dioxide (CO₂)
 - mortality.

Other limiters

English language.

Human studies.

Grey literature, databases of theses and conference proceedings were not included.

Exclusion criteria

- Isolated case reports.
- Adult-only studies.
- Inpatient studies conducted entirely in PICU, NICU, emergency or in-patient ward settings.
- Theatre or post-operative studies.

Information Sources

The following information sources were searched from inception to 23/03/2017:

- **Electronic databases**

MEDLINE via PubMed, EMBASE (via Scopus), Cochrane Central Register of Controlled Trials (CENTRAL), African Index Medicus and Web of Science Citation Index.

- **Trials registries**

A search was performed of the World Health Organisation Trials Registry ICTRP. This is a searchable database containing weekly updates of all major national and international trials registries, including the:

- Australian Trials Registry;
- European Trials Registry;
- UK Trials Registry; and
- US Trials Registry.

- **Searching other resources**

Reference lists of included studies were reviewed by BC for additional relevant citations.

Search terms

The search was iterative and included, but was not limited to, the following keywords, PubMed MeSH terms and text words in combination or alone, as appropriate to the search engine of the database in question:

- **Keywords:**

Non-invasive ventilation, high-flow nasal cannula, nasal continuous positive airway pressure, non-invasive positive pressure ventilation, acute respiratory distress, infant, child.

- **PubMed MeSH terms:**
 - noninvasive ventilation
 - continuous positive airway pressure
 - infant OR child OR infant, newborn
 - intensive care units, OR intensive care units, neonatal;
 - emergency treatment OR emergency service, hospital OR emergency medical services; and
 - transportation of patients.

- **Text:**
 - neonate OR children OR infant OR pediatric OR paediatric;
 - [high AND flow AND nasal] OR [high-flow AND nasal];
 - [nasal AND continuous AND positive AND airway AND pressure];
 - [(non-invasive OR noninvasive) AND positive AND pressure AND ventilation];
and
 - transport OR transfer OR inter-facility OR inter-facility OR retrieval.

Search

Search dates

The systematic search was conducted between 15-23 March 2017. As an example, the detailed search strategy for PubMed is shown in Appendix E. Regular updates for the searches in MEDLINE via PubMed, EMBASE (via Scopus), African Index Medicus and Web of Science Citation Index were reviewed for new references until 1st August 2017.

Master list and duplicate removal

A list of studies identified from all databases was merged into a master list on Mendeley reference manager and duplicates were excluded. The PRISMA flowchart (Figure 7 Chapter 5: Results) shows visually the number of citations originally identified in the search and the numbers excluded with reasons.

Initial review

The list of identified titles, some accompanied by abstracts, was reviewed by two independent reviewers (BC & BR). At this stage, any studies with obvious ineligibility or irrelevance were removed. Further duplicate reports of the same studies were identified and

removed at this stage. For any studies where there was uncertainty as to eligibility, the study passed through to the next round, for review of the full-text version of the article.

Full-text review

Full-text versions of studies which were not excluded by this stage were reviewed independently by BC & BR to formally assess their compliance with eligibility criteria.

Dispute procedures

In cases where BC & BR had different opinions regarding eligibility, consensus was reached through discussion.

Data-Collection Process

A standardised data extraction form was piloted and developed by BC, who then completed the fuller version of this form with 40 data items (Appendix F). A shorter version, containing 22 core data items for demographics and primary and secondary outcomes, was completed by BR (Appendix G). The 22 core data items were compared for consistency and discrepancies resolved by discussion between the two reviewers.

Statistical Analysis

Summary measures

The summary measures used were comparisons of measures of central tendency and variation around these, as reported by the included studies.

Additional analyses

Inter-rater agreement

The degree of agreement between reviewers' ratings for individual studies using the adapted QA tool was assessed using agreement Intra-Class Correlation (ICC) with a two-way underlying ANOVA model.

Intubation within 24-hours

Sub-group analysis was done to compare the proportion of children requiring intubation within 24 hours of transport on CPAP versus HFNC. This was done using cross-tabulation and

the Chi-square test. Confidence intervals for the calculated proportions were calculated using binomial as underlying distribution.

Quality Assessment of Studies

Quality Assessment Hierarchy

The following published QA tools were identified as appropriate for use with the study designs listed:

- Randomised and Quasi-randomised controlled studies: the Cochrane Risk of Bias tool(120),
- Non-randomised studies of interventions: the Cochrane Collaboration tool: Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I).(121,122)
- Observational studies: the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklists for cohort, case-control and cross-sectional studies(123)
- Case-series studies: Moga Quality Appraisal Tool for Case-series(124)

Adaptation Process for Quality Assessment Tool

A generic QA tool for use with observational studies researching NIV use in transport, was developed to appraise studies not conforming to evaluation by any of the standard QA tools for observational studies. The need for this tool became apparent as there was a lack of detail provided in the selected studies, which would have been required to complete the STROBE cohort checklist, which was deemed the best-fit QA tool.

The generic tool was adapted from the 18-item Moga Quality Appraisal Tool for Case-series(124) (see Appendix B). The authors are clear in their discussion and conclusion that the tool they have developed is a guide and should be modified by systematic reviewers according to the criteria most relevant for their field. They also stipulate that whilst they did not incorporate a score or grading system, future users of this QA tool may wish to stipulate cut-offs for distinguishing low- from high-quality studies.(124)

The adapted QA tool for this review, has 20 criteria gauging quality across domains including study design, participant selection, study procedures and completeness of reporting (see Appendix C). The adaptation process involved removal of criteria considered irrelevant, unanswerable or repetitive, with insertion of new or modified criteria, specific to NIV use in transport.

Examples of deleted criteria include: 'Were the case series collected in more than one centre?' And 'Did patients enter the study at a similar point in the disease?' An example of modified criterion is: 'Did the authors describe the intervention?' This was replaced with three criteria: 'Was the method of NIV generation clearly described in the study? (Device details, manufacturer, model etc.); 'Was the type of NIV interface used described? (nasal/nasopharyngeal prongs, mask, helmet etc.)' and 'Is there adequate description of the NIV protocols used? (indications, contraindications, pressure/flow etc.)' Repetitive criteria such as 'Was loss to follow-up reported?' And 'Was the length of follow-up clearly described/reported?' were combined into a single new criterion: 'Was there any follow up after the immediate transport period?' All deleted, new and modified criteria are highlighted in Appendix B and C.

Each quality criterion was awarded a zero, half-point score or one point depending on whether the criterion was not met, partially met or fully met. Thus, the highest score possible was 20 and the lowest, zero. The scores were converted to a percentage and studies with percentage scores of 0-49% were considered poor quality, those scoring 50-74%, as good, and those scoring over 75%, high quality.

Quality Assessment Process

Quality assessment was done independently by two reviewers (BC & BR). The scores were compared and consensus on final scores reached by discussion (see Table 15 Chapter 5: Results).

CHAPTER 5: RESULTS

Description of Studies

Results of the search

A total of 1287 records were identified, of which 12 studies met inclusion criteria (see Figure 7). Following quality assessment, eight studies(7,8,125–130) were included and four studies were excluded (131–134).

The eight included studies involve 858 paediatric patients transferred on NIV: 708 on CPAP and 150 on HFNC. Patient ages were reported using different scales between the studies, with some giving age in weeks of GA and others in days or months (see Table 14).

No RCT, QRCT or NRSI studies addressing the research question were found. All included studies are observation in design: seven used a retrospective record review methodology(7,8,125–128,130) and one was a prospective observational study.(129) The study durations were between 18-48 months and the number of NIV transports per study varied from 31-207.

Figure 7: Search and selection of studies

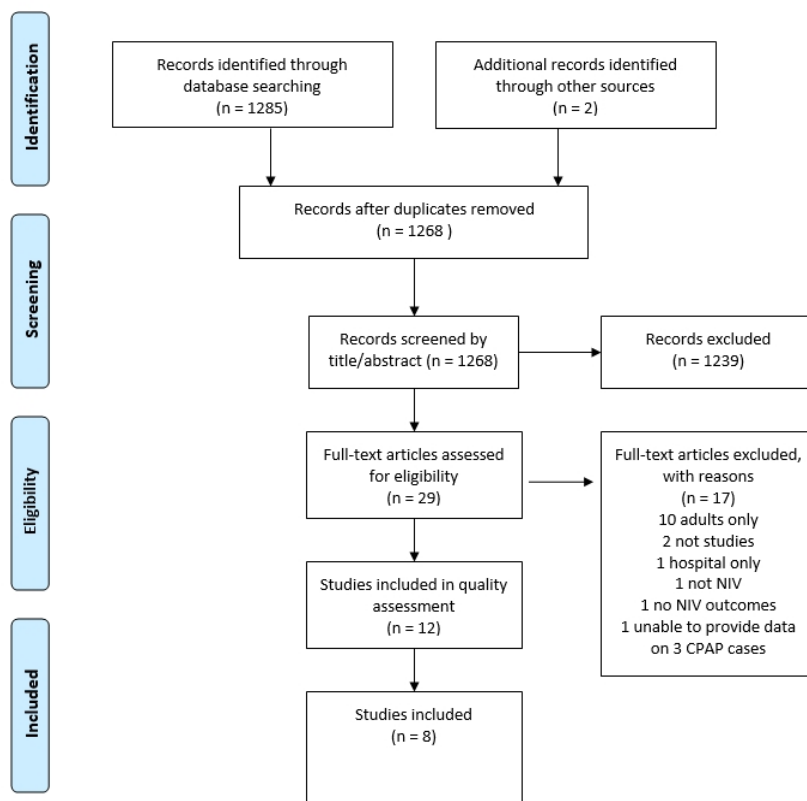


Table 14: Study details and patient demographics

Study ID	Number of patients & type of NIV	Location	Methodological characteristics	Study Dates	Study duration (months)	Age or Gestational Age (GA) (mean,SD) ² (median,IQR) ³	Diagnosis
Baird-2009	18 ¹ CPAP	New York State, USA	Retrospective record review	Jan 2005 to June 2006	18	0.8 ± 0.7 months ²	CNS 10 (40%), Pulmonary 10 (40%), CHD 4 (16%)
	13 ¹ BiPaP					6 ± 5 months ²	
Bomont-2006	100 CPAP	Cambridge & East of England, UK	Retrospective record review	July 2003 to March 2005	21	28.3 days ± 24.3	Not documented
Fleming-2012	51 CPAP	Victoria, Australia	Retrospective record review	Jan 2003 to June 2007	54	54 days ± 39 ²	Bronchiolitis 54 (100%)
Jani-2014	44 CPAP	New South Wales, Australia	Retrospective record review	Jan 2009 to Dec 2010	24	Gestational age 30 wks ± 27-31 ³	30 (60%) had CXR of RDS, 19 (38%) normal CXR and 1 (2%) did not have a CXR
Millan-2017	50 CPAP 58 BiPAP	Catalonia, Spain	Prospective observational	01/11/2010-01/03/2013	28	3.4 months ± 1.2-1.7 ³	Bronchiolitis 63 (58%), wheezing 16 (15%), Pneumonia 16 (15%).
Murray-2008	207 CPAP	Victoria, Australia	Retrospective record review	01/01/2004-01/11/2005	22	1 day ± 0-175 ³	RDS 131 (61%), Bronchiolitis 27 (12%), CLD 19 (9%)
Resnick-2010	167 CPAP	Western Australia, Australia	Retrospective record review	01/02/2002-01/12/2004	34	Gestational age 37 wks ± 32-41 ³	RDS 311/369, MAS 19/369, Pneumothorax 15/369
Schlapbach-2014	150 ¹ HFNC	Queensland, Australia	Retrospective record review	01/01/2009-31/12/2012 ¹	48	6.2 months ± 0.3-23 ²	Bronchiolitis 115(77%), Respiratory NON-bronchiolitis 25(17%), Neuromuscular 3(2%)

CPAP Continuous positive airway pressure; BiPAP Bilevel positive airway pressure; HFNC High flow nasal cannula; CNS Central Nervous System; CHD Congenital Heart Disease; CXR chest radiograph; RDS Respiratory Distress Syndrome; CLD Chronic Lung Disease; MAS Meconium Aspiration Syndrome.

¹ Thirty-one transports in 25 patients

² Results given as mean, standard deviation

³ Results given as median, inter-quartile range

Quality assessment of included studies

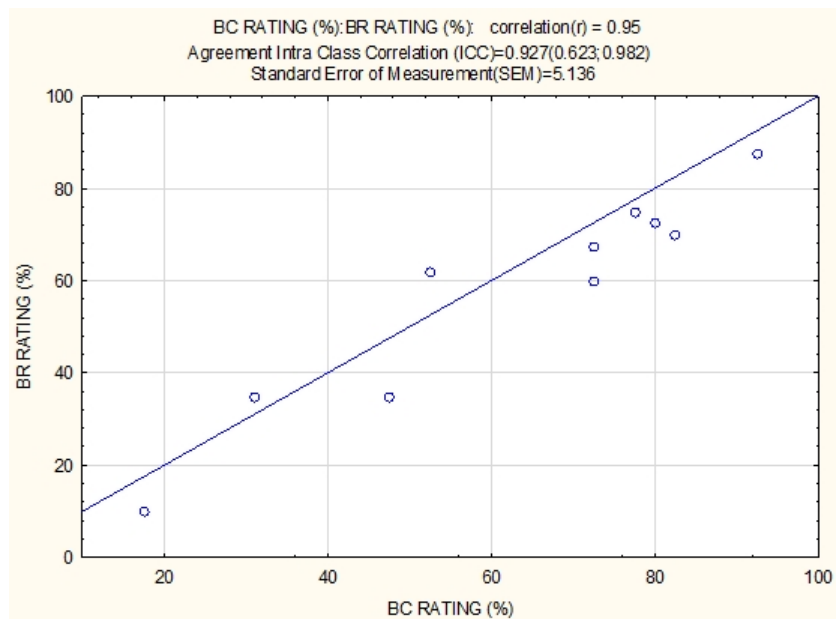
Two reviewers independently evaluated all eligible studies using the adapted QA tool (see Appendix C). The quality rating scores for independent reviews of each study and the agreed consensus scores are given in Table 15. Studies with a score of less than 50% were excluded.

Table 15: Quality assessment ratings of studies

Study ID	BC rating (%)	BR rating (%)	Consensus scores (%)	Decision
BAIRD-2009	52.5	62.0	55.0	Include
BOMONT-2006	72.5	60.0	57.5	Include
BOYLE-2014	17.5	10.0	12.5	Exclude
FLEMING-2012	82.5	70.0	82.5	Include
JANI-2014	92.5	87.5	92.5	Include
KAPADIA-2012	31.0	35.0	30.0	Exclude
MILLAN-2017	77.5	75.0	77.5	Include
MURRAY-2008	80.0	72.5	77.5	Include
OFOEGBU-2006	47.5	35.0	40.0	Exclude
RESNICK-2010	72.5	67.5	72.5	Include
SCHLAPBACH-2014	82.5	70.0	75.0	Include
SIMPSON-2004	25.0	BC only	25.0	Exclude

There was excellent inter-rater agreement, with a strong positive correlation between the scores given by the two reviewers overall ($r=0.95$) as well as good intra-class correlation (ICC = 0.93) see Figure 8. There was a low standard error of measurement (SEM = 5.1).

Figure 8: Inter-rater agreement using adapted quality assessment tool



Details of included studies

Baird et al.(125) studied 32 transports in 26 children, aged 1 month to 18 years, who were transferred into or out of a regional PICU. One patient failed NIV and was transported on room air, and they report details of 31 transports of 25 children. None of the patients had acute respiratory distress syndrome and nine children (36%) were NIV-dependent for at least one month prior to transport. Exclusion criteria included cardiopulmonary arrest, shock, head/neck trauma and those with ARF unable to protect the airway. It is interesting to note that patients with chronic respiratory failure and weak or absent cough were eligible for inclusion.

This study reported on two modes of NIV during transport: CPAP and BiPAP. NIV was delivered using the Pulmonetics LTV-1000 (Minneapolis, MN) CPAP mode (n=15) or CPAP with pressure support mode (BiPAP n=12) and the Bio-Med Devices MVP-10 (Guilford, CT) CPAP mode (n=3) or CPAP with pressure control mode (BiPAP n=1).(125)

Bomont et al.(126) studied 100 NIV transports in neonates performed by an acute neonatal transport service, covering 18 hospitals with varying levels of NICU service. These cases were identified from a database of transfer requests, through the criterion of requiring nasal CPAP at the time of referral. Patients were separated into 'emergency team' transfers, which were conducted by a doctor-nurse team (n=84), and 'nurse-led' transfers (n=16). Inclusion and exclusion criteria were not specified, except by reference to their standard criteria for emergency or nurse-led transfers. Continuous positive airway pressure was delivered using the integral Babylog 2000 ventilator in a Draeger 5400 transport incubator (Draeger Medical UK Limited, Hemel Hempstead, Hertfordshire, UK).

Fleming et al.(127) identified 51 infants with suspected bronchiolitis from a neonatal transport database. These infants were managed with CPAP during retrieval in their defined study period. Infants who were transferred on oxygen alone or IPPV were excluded, as were those with respiratory failure from causes other than bronchiolitis. Continuous positive airway pressure during transport was delivered using a Stephan Reanimator 120 Ventilator (Stephan GMBH, Gackebach, Germany).

Jani et al.(128) reviewed an electronic database of transfers performed by a regional neonatal transfer team to identify 50 infants, aged less than 32 weeks GA and less than 72 hours of age, who had been transferred on CPAP during the study period. Infants were excluded if they had already been transferred from another unit or if they received IPPV or oxygen only during transport. The authors state that 'nasal CPAP is delivered using the Fisher

and Paykel infant nasal interface', but the device used to drive gas flow is not specified. It is specified that the results are displayed as median, unless stated otherwise, but the authors do not state what measure of spread around the median is used, i.e. interquartile range (IQR) or full range. For the purposes of this study it will be assumed that the IQR has been given.

Millan et al.(129) report on 288 children with ARF transported by the two transfer teams of a tertiary PICU: 54 (19%) transferred on IPPV; 126 (44%) on oxygen alone or nebulisation, and 108 (37%) on NIV. The results of this study are reported in three separate periods, reflecting the evolution of a local NIV protocol. The protocol was supposed to be available in the supplementary materials for this article, but the materials were not found at the journal website. The study author was contacted and provided the protocol and additional information by email. Some of the information provided in this section comes from this personal communication with Dr Nuria Millan. Non-invasive ventilation in this study was provided by: the Oxylog 3000 (Draeger Medical, Luebeck, Germany) for 38 patients weighing over 10kg; the Crossvent 2+ (Bio-Med Devices, Guilford, Connecticut, US) for 67 transfers in patients weighing less than 10kg and three children were transported using their home ventilators [personal communication from Dr Nuria Millan].

Indications for NIV were Type 1 or Type 2 ARF with definitions and criteria given in the protocol. General contraindications for NIV were: undrained pneumothorax; bullous pneumopathy; vocal cord paralysis; hemodynamic instability; Glasgow Coma Scale less than or equal to 12; or progressive decrease; active gastrointestinal bleeding, recent gastric or esophageal surgery, vomiting or bowel obstruction and patients with sinus infection, pneumoencephalus on CT scan or facial trauma. Specific contraindications for NIV in transport were patients with: NIV in the emergency room; without appropriate improvement on arrival of transport team; inability to manage secretions; saturation/ $\text{FiO}_2 < 150$ at 30 minutes if ARDS is suspected; requiring settings above IPAP 18/ EPAP 8 and $\text{FiO}_2 > 0.60$, or CPAP 10 before leaving the referring hospital (15- 30 minutes on NIV); no improvement in work of breathing after 15-30 minutes on NIV; upper airway obstruction (laryngitis, foreign body) and poorly cooperation despite sedation [personal communication from Dr Nuria Millan].

Murray et al.(7) searched a computer database of all neonatal transports done by a specialised neonatal transfer team where CPAP was used. They identified 220 patients treated with CPAP, of whom 13 were intubated prior to transport. The remaining 207 infants were transported on CPAP. Four of these were considered CPAP failures, on the basis of *a priori* failure criteria. No exclusion criteria were stipulated for this study. Nasal CPAP was

delivered using a Stephan ventilator (the make, model and manufacturer are not specified). The authors state that results would be presented as median (range), but they do not state what measure of spread around the median is used, i.e. interquartile range (IQR) or full range. For the purposes of this study, it was assumed that the IQR has been given.

Resnick et al. (Resnick 2010)(8) reviewed their transport database for infants aged over 32 weeks GA and less than 48 hours of age with acute respiratory distress. They identified 369 infants (excluding those with congenital abnormalities) during the study period. The mode of ventilation was IPPV in 107 (29%); CPAP in 167 (45%) and cot oxygen in 95 (26%). The Stephan transport ventilator (F120 Reanimator, F. Stephan GmbH, Gackebach, Germany) in CPAP mode was used to deliver NIV in this study. The authors state that results will be presented as median (range), but they do not state what measure of spread around the median is used, i.e. interquartile range (IQR) or full range. For the purposes of this study, it was assumed that the IQR has been given.

Schlapbach et al.(130) compared IPPV rates during transport of children aged less than two years to a PICU, across two four-year periods before and after the introduction of HFNC. A total of 793 infants were transported during the eight-year study period. In the pre-HFNC period there were 331 transfers [163 (49%) on IPPV, 142 (43%) on oxygen, 23 (7%) on NIV and 3(1%) on HFNC. In the post-HFNC period there were 462 transfers [162 (35%) on IPPV; 140 (30%) on oxygen; 10 (2%) on NIV and 150 (33%) on HFNC. Only transfers performed by the in-house RT were included – any transfers conducted by other RTs were excluded (number not provided); no other exclusion criteria were specified. The authors state that HFNC was delivered using a heated humidifier device (Fisher & Paykel Healthcare Ltd., Auckland, New Zealand). During the first four-year study period, there were small numbers of patients transferred on NIV (n=23) and HFNC (n=3), and insufficient information for analysis is supplied for these patients. Similarly, there is inadequate information provided on the 10 patients transferred on NIV during the second four-year study period. Therefore, only the 150 HFNC transfers conducted in the second four-year period are included in this review.

Details of excluded studies

Boyle et al.(131) identified 31 transports on HFNC over a five-month period from a transport database of their neonatal transport service in the UK. They divided transports into elective (repatriation, nurse-led) and emergency transfers (two clinicians). The data evaluated included changes to HFNC flow rate and AEs during transport.

Kapadia et al.(132) reported on nurse-led, single-clinician CPAP transfers by the same UK neonatal transfer services as in the Boyle et al. study, for the period 2009 (dates not given). They identified 47 transfers done on CPAP. They recorded clinical, technical and transport related AEs during transfer.

Ofoegbu et al.(133) reviewed 31 neonatal ‘back-transfers’ to base hospitals from one NICU in the UK over a 23-month period. They report on temperature control and technical AEs during transport. The study involved telephonic follow-up two weeks after transfer.

Simpson et al.(134) reported on seven CPAP transfers in six neonates over a one-year period. All but one infant were reported as stable on CPAP ‘for sometime’ prior to transport. No detail is given on the variables recorded during transport.

These four excluded studies were all published as short reports: three studies were reported in Acta Paediatrica(9,10,11) and the fourth was published as a letter in the journal Archives of Diseases in Childhood, Fetal and Neonatal Edition.(134) All four excluded studies were reported in less than 700 words and with three references or less. Upon QA evaluation of the study reports, they scored below inclusion level, primarily because they contained insufficient information for analysis in this review.

Effects of Intervention

Primary outcomes

Intubation or escalation of non-invasive ventilation during transport

Overall, 3/858 (0.4%) children transported on NIV required either intubation or escalation of the level of NIV, during transfer (see Table 16). Intubation during transport occurred in 1/708 (0.1%) CPAP patients. There were 0/150 reported intubations during transfer on HFNC. However, escalation from HFNC to CPAP or B_LCPAP was needed in 2/150 (1%) during transfer.

The authors of the study in which the one child was intubated during CPAP transfer, state in their results section, that the child was intubated ‘due to a fast progression of the ARF’.(129) They add: ‘A post-transport analysis of this subject’s clinical chart suggests that this subject had ongoing ARDS, which should have been detected before leaving the referring hospital because it is an important contraindication for NIV during transport in our protocol.’(129) No further demographic, clinical or transport details or outcomes are provided for this patient.

Table 16: Primary outcomes

Study ID	Intubation [or NIV escalation] ¹ during transport	Intubation after transport Number (%)	Timing of intubation [or escalation of NIV] ¹ Number (%)	Adverse events during transport Number (%)						
				BVM	CPR	Apnoea	Desaturation	Bradycardia	Hypotension	Air Leak
Baird-2009 (N=31)	0	6/17 (35%) ²	3(50%) <24h ² 3(50%) >24h ²	8(26%) ³	0	ND	8 ³	Up to 8 ³	ND	ND
Bomont-2006 (N=100)	0	ND	ND	0	0	2 ⁴	1 ⁵	3 ⁶	ND	ND
Fleming-2012 (N=51)	0 ⁷	5(10%)	5(100%) <24h	0 ⁷	0 ⁷	0 ⁷	0 ⁷	0 ⁷	0 ⁷	ND
Jani-2014 (N=44)	0	7(16%)	2(29%) <24hr 5(61%) 1-7d	0	ND	ND ⁸	ND	ND	ND	0
Millan-2017 (N=108)	1	23(21%)	4(17%) <2h, 11(48%) 2-12h, 8(35%) >12h	0 ⁹	0 ⁹	0 ⁹	0 ⁹	0 ⁹	0 ⁹	0 ⁹
Murray-2008 (N=207)	0	32(16%)	28(88%) <24h & 4(12%) >24h (11 for surgery)	0	ND	ND	ND	ND	ND	ND
Resnick-2010 (N=167)	0	22(13%)	22(100%)<24h	ND	ND	ND	ND	ND	ND	0
CPAP Total	1/708 (0.1%)	94/594(16%)¹⁰	60/500(12%)¹¹	8/334(2%)¹²	0/290(0%)¹²	-	9/290(3%)¹²	11/290(4%)₁₂	-	-
Schlapbach-2014 (N=150)	2 ¹³	3(2%)	3(2%) <24h, [9(6%) escalated to NIV<24h] ⁹	ND	0	ND	ND	ND	ND	0
Overall Total	3/858 (0.4%)	97/744 (13%)	63/650 (10%)¹¹	8/334(2%)¹²	0/290(0%)¹²	-	9/290(3%)¹²	11/290(4%)₁₂	-	-

BVM Bag Valve Mask ventilation; CPR Cardio-Pulmonary Resuscitation; ND, Not Documented

¹ In CPAP only studies escalation was to intubation and IPPV but for HFNC study escalation from HFNC could be to other NIV (e.g. CPAP or BiPAP) or to intubation and IPPV

² Escalation to intubation was only reported for the 17/31 patients transferred into the study hospital. Intubations occurred at 3,7,12,25,48 & 84hr after transport.

³ Authors state that 'Airway suctioning and/or use of BVM during transport were performed on 8/31 transports because of episodes of desaturation, occasionally with bradycardia'

⁴ 1 apnoea in doctor/nurse team and 1 apnoea +bradycardia in nurse-led team

⁵ 1 patient had bradycardia and desaturation – this patient is recorded in both bradycardia and desaturation results

⁶ 1 bradycardia and 1 bradycardia and desaturation in doctor/nurse team and 1 apnoea and bradycardia in nurse-led team

⁷ Assumed to be zero as the study authors state: 'There were no adverse events recorded in patients transferred on CPAP'

⁸ Authors report 6 cases of apnoea in their general description of the whole group, but it is not clear if these occurred before, during or after transfer

⁹ Apart from 1 patient intubated during transport and 3 cases of NIV/CPAP interface authors state 'No other complications resulted from NIV/CPAP in our subjects'.

¹⁰ Denominator excludes 14/31 patients from Baird et al that were transferred out of their PICU and for whom there was no post-transfer intubation data

¹¹ Excluding results from Millan et al as they did not report intubation <24 hours as an outcome

¹² Adverse events summarized only where at least 4 of 7 CPAP studies reported data on this event, denominator varies by number of participants per study

¹³ 2 patients were escalated to either CPAP or BiPAP during transfer and a further 9 were escalated to CPAP or BiPAP within 24 hours of transport

Intubation or escalation of non-invasive ventilation after transfer

Intubation post-transfer is reported in seven studies (n= 744): six CPAP studies (n=594) (7,8,125,127–129) and one HFNC study (n=150)(7,8,125,127–130). Overall, 97/744 (13%) of children were intubated during the varying follow-up periods of these studies. Not all studies reported timing of intubation after transfer, from studies where this parameter was reported, intubation occurred within 24 hours of transfer in 63/650 (10%) patients overall (see Table 16).

Millan et al.(129) reported intubation time-frames differently from other studies, describing the overall number intubated and those intubated within two hours and 2-12 hours of transfer. The remaining five CPAP studies (1,3,4,6,7) described the number of patients intubated within 24 hours and after 24 hours from transfer, either directly or in a manner that permitted this to be calculated. Data from these five CPAP transfer studies (n=500; 72 intubations) (1,3,4,6,7) shows that 60/500 (12%) of these patients were intubated within 24 hours of transport.(7,125,127,128) Following transfer on HFNC, 3/150 (2%) of patients were intubated within 24 hours and a further 9/150 (6%) were escalated to either CPAP or B_LCPAP. The odds of intubation within 24 hours was significantly higher for CPAP transfer 60/500 (12%) compared with HFNC 3/150(2%): OR (95% CI) 6.68 (2.40 – 18.63), p=0.00003.

Individual studies reported post-transfer intubation rates of between 10-35%. The highest intubation rate was from Baird et al.(125) This study reported intubation following arrival at destination only for the 17/31 patients that were transferred into their PICU. This particular study had a high proportion [9/25 (33%)] of long-term NIV-dependent patients prior to transfer as well as a high rate of chronic diagnoses, including central nervous system (40%) and congenital heart disease (16%) patients.

Adverse events during transport

The reporting of AEs during transport was incomplete and variable amongst the studies. Adverse events during transport were not described in the HFNC transfer study.(130) Therefore, information on AEs during transport comes from the CPAP transfer studies(7,8,125–129)(see Table 3).

To illustrate the level of AE reporting, the following quotes contain either the majority, or all of the information describing AEs during transport, in the respective studies:

- Murray et al.(7): 'No patient required bag or mask ventilation or intubation during transport, and none had problems with oxygenation that warranted discontinuation of NCPAP.'
- Resnick et al.(8): 'The incidence of pneumothorax did not increase with the increasing use of CPAP, with no pneumo-thoraces occurring during transport.' Also: 'There were no deaths during retrieval or in NICU, within the CPAP or cot O₂ groups.'
- Jani et al.(128): 'None of the study infants developed pneumo-thorax either during transfer, or after admission.' Also: 'None of the 44 study infants died during transfer, or following admission.'

Beyond these, some authors made generic statements such as 'there were no adverse events recorded'(127) or 'no other complications resulted from NIV/CPAP in our subjects.'(129) For the purposes of this study, in cases where authors used general descriptions such as 'no adverse events experienced', it was assumed that these events did not occur.

Results for AEs during transport were collated only where at least four of the seven CPAP studies reported on the AE, either directly or in a manner from which the presence or absence of the AE could be deduced. The specific adverse events that were reported during transport include BVM 8/334(2%), desaturation 9/290(3%) and apnoea 11/290(4%) (see Table 16).

Two studies reported greater details of specific adverse events during transport. Baird et al.(125) state: 'Airway suctioning and/or use of bag–valve–mask ventilation during transport were performed on eight of 31 (26%) transports because of episodes of transcutaneous oxyhemoglobin desaturation, occasionally with bradycardia; bag–valve–mask ventilation was used between attempts at airway suctioning to help restore and pre-serve oxygenation while disconnected from NIV, and in one patient to allow adjustment and repositioning of the NIV interface as well as a change in NIV air- way pressures. All desaturation episodes responded to treatment, allowing the resumption of NIV during transport.'

Bomont et al.(126) had five cases of adverse events during transfer. Three adverse events occurred during doctor-nurse team transfers: one apnoea, one desaturation and one bradycardia and desaturation, all of which responded to stimulation. Two adverse events occurred during nurse-led team: one apnoea with bradycardia requiring stimulation and one repositioning of nasal prongs with no associated deterioration.

Secondary outcomes

Heart rate

Two studies reported on HR measurements at different time-points during the transfer process. Baird et al.(125) report on vital signs from 31 NIV transport. They found no change in HR mean(SD) taken prior to transport, compared with values at the end of transport (143(21) vs 138(20); p=0.45). Jani et al.(128) compared HR 'at first look' and 'at stabilisation' for two groups: 37/44 successfully transferred on and 7/44 CPAP failure patients. At both time-points the HR median(IQR) values were not significantly different: first look 145 (100-176) vs 144 (128-158); p=0.54, and at stabilisation: 146 (113-187) vs 142 (123-159); p=0.65.

Respiratory rate

The same two studies reported RR during transport. Baird et al.(125) found no difference in RR mean (SD) measured prior to transport, compared with the end of transport: 41(9) v 37(8); p=0.36). Jani et al.(128) found no difference in RR values at first look and at stabilisation for 37/44 CPAP success cases vs 7/44 CPAP failures. Respiratory rate median (IQR) values at first look were 51(27-86) vs 45(42-80); p=0.75, and at stabilisation: 47.5 (21-82) vs 50(36-68); p=0.0.70.

Oxygen saturation

Only one study reported SaO₂(%). Baird et al.(125) found no difference in SaO₂ mean (SD) at the start compared with the end of transport: 97(6) vs 98(1); p=0.9.

Work of breathing

No study reported on parameters of WOB during transport.

Fractional inspired oxygen

This was reported in a variety of ways in five of eight NIV studies.(7,8,125,127,128) Baird et al.(125) stated that FiO₂ varied widely between 0.21-100. Fleming et al.(127) found that the FiO₂ (mean, SD) initially 0.62 (0.29) was statistically higher compared to FiO₂ (mean, SD) 0.4 (0.14), on arrival at the destination (p<0.001).

Jani et al.(128) had measures of FiO₂ recorded at three time points: at first look, at stabilisation and at admission to the receiving facility. These measures were compared between the 37/44 CPAP successes versus the 7/44 CPAP failures. They found statistical

difference only in the admission FiO_2 (median, IQR) 0.21(0.21-1.00) in CPAP success and 0.3 (0.21-0.3) in CPAP failures ($p < 0.05$). Failure of nasal CPAP in this study was defined as: '(1) need for bag-and-mask ventilation while receiving NCPAP, (2) continuing moderate or severe respiratory distress, increasing inspired concentration of oxygen while receiving NCPAP or $\text{pCO}_2 > 55$ mmHg while on NCPAP or (3) any reason to intubate before transport, during transport, or seven days following admission related to RDS.'(128)

Murray et al.(7) found the FiO_2 (median, IQR) was significantly lower at the end of transport than at the beginning: 0.45 (0.21-1.0) vs 0.34 (0.21-1.0); 95% CI 0.05-0.12; $p < 0.001$). They report that 173 infants had decreasing FiO_2 during transport, with 9 (4%) having an increase in FiO_2 during transport: five of these involved an FiO_2 rise of more than 0.1 and four, a rise greater than 0.2. Of these nine patients, 5/9 (56%) were never intubated, three (33%) were intubated less than 24 hours after transfer, and 1/9 (11%) was intubated for surgery.

Resnick et al.(8) found that the median (IQR) FiO_2 of all 167 CPAP transferred patients was initially 0.47 (0.21-0.75) compared with 0.4 (0.21-0.75) ($p < 0.001$) after transfer. Amongst the 145/167 patients successfully transferred on CPAP, they found significantly higher FiO_2 at initial stabilisation compared with FiO_2 following transfer: 0.45(0.21-1.0) vs 0.4 (0.21-0.75) $p < 0.001$.

Carbon dioxide measurement

This was reported in three studies. Fleming et al.(127) had transcutaneous CO_2 (tCO_2) data available for 40 patients with (mean, SD) tCO_2 of 49(17) 'during stabilisation' and 45 (11) at the 'end of retrieval'.

Jani et al.(128) report blood gas pCO_2 measurements from 28 patients who had median(IQR) 48mmHg (27-68); 7 of these patients had pCO_2 greater than 55mmHg, of whom one required IPPV within 24 hours and one after 24 hours following admission.

Murray et al.(7) report tCO_2 for a total of 220 patient, 203 of whom were transferred on NIV and 13 of whom were intubated prior to transport. They found overall that tCO_2 (median, IQR) at the start and end of transport both to be 45mmHg ($p = 0.7$). The tCO_2 increased by more than 7mmHg in 16(7%) patients, with four of these having $\text{tCO}_2 > 60$ mmHg and of these

4/16 (25%) were intubated. The authors describe one of these intubations as occurring before transfer and three within 24 hours of arrival at destination. Thus, 3/15 (20%) patients transferred on NIV who were found to have rising tCO₂ were intubated within 24 hours of arrival at destination.

Degree of acidosis on blood gas analysis

This was not reported in any of the studies.

Mortality

Mortality amongst study patients was specifically mentioned in three studies. Jani et al.(4) stating that 'none of study infants died during transfer, or following admission'. Resnick et al.(8) reported that 'there were no deaths during retrieval or in NICU, within the CPAP or cot O₂ groups'. Schlapbach et al.(130) said no patients died 'during the entire study period'.

Additional analyses

During this study, it became clear that additional interesting information, which had not been specified in the objectives of this research was available from several included studies. Much of this information has not been previously reported in the context of NIV during transport of children and therefore, as it is novel, interesting and potentially useful to clinicians and researchers in this field it is presented below.

Non-invasive ventilation settings during transport

Some degree of information regarding the settings used for NIV during transport was reported in seven studies (see Table 17). (7,8,125,127–130) The CPAP pressure varied between 5-10 cmH₂O and HFNC was given as 2L/kg/min, with B_LPAP values varying. There was little or no information given regarding NIV protocols or adjustments made during transport. Settings at the start and end of transport were not reported in any study.

Table 17: Non-invasive ventilation methods

Study ID	Type of NIV (Number, N)	Method of NIV generation	NIV Interface (N, where given)	NIV started by retrieval team (N, %)	NIV settings for transport Mean(\pm SD) ¹ Median(\pm IQR) ²
Baird-2009	CPAP (18) BiPAP (13)	Ventilator	Nasal prongs (27) 'nasal or face-mask' (4)	7/31 (23%) CPAP-6 BiPaP-1	CPAP 5cm BiPAP 10-20cm
Bomont-2006	CPAP (100)	Ventilator	Bi-nasal prongs (Argyle)	0/100 (0%)	ND
Fleming-2012	CPAP (51)	Ventilator	Bi-nasal prongs (Hudson)	34/51 (67%)	7cm (1.2) ¹
Jani-2014	CPAP (44)	Flow Driver ³	Bi-nasal prongs (Fisher & Paykel)	23/50 (46%) ⁴	6cm (5-7cm) ²
Millan-2017	CPAP (50) BiPAP ⁵ (58)	Ventilator	Bi-nasal prongs 37 (34%) ⁶ Oronasal interface 35 (32%) ^{6,7} Nasopharyngeal tube 36 (25%) ⁶	102/108 (94%)	CPAP ⁸ 5-10cm BiPAP ⁸ 18 (5-8)cm BiPAP ⁸ IPAP 14cm EPAP 6cm
Murray-2008	CPAP (207)	Ventilator	Bi-nasal prongs (Hudson)	133/220 (60%) ⁹	7 (5-10) ²
Resnick-2010	CPAP (167)	Ventilator	Bi-nasal prongs (Hudson)	167/167 (100%)	5-6cm ¹⁰
Schlapbach-2014	HFNC (150)	Flow driver	Bi-nasal prongs (Fisher & Paykel)	ND	2L/kg/min ¹¹

NIV, non-invasive ventilation; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; ND, not documented

¹ Results given as mean, standard deviation (SD)

² Results given as median, inter-quartile range (IQR)

³ Device details not fully specified but assumed to be a flow-driver

⁴ Total of 50 patients, 6 of whom failed CPAP, 44 transferred on CPAP

⁵ Authors use terminology CPAP and NIV interchangeably yet they describe 50 patients in CPAP and 58 'NIV' confirmed in personal communication that CPAP is one level of pressure whereas NIV refers to bi-level pressure

⁶ Personal communication from author

⁷ Personal communication from author: six different types of oro-nasal masks were used, some were vented but these were adapted to be non-vented for the study

⁸ In the methods section, the authors state: 'CPAP values ranged from 5-10cm H2O pressure; NIV included maximum IPAP 18cm H2O and EPAP of 5-8cm'. For NIV authors report median IPAP & EPAP reported in results section.

⁹ For all 220 patients in whom CPAP was initiated (207 transferred on CPAP failed CPAP and transferred on IPPV)

¹⁰ In the methods section, the authors state: 'CPAP pressure was commenced at 5cm H2O, with only a small number receiving pressures of 6cm H2O.'

¹¹ In the methods section, the authors state: 'HFNC (defined as 2L/kg/min flow with the use of nasal cannula)'

Non-invasive ventilation started by retrieval team

The number of children in whom NIV was commenced by the retrieval team was reported in five studies (7,8,125,127,128) and could be deduced in a further two (126,129) studies. In two of these studies there was no option in terms of RT commencing of NIV/non-NIV for transport: in the Bomont et al.(126) study, cases were all identified by the fact that they were on CPAP at the time of referral, and in the Resnick et al.(8) study, only cases where the RT had opted to commence NIV were included. In the remaining studies, where the RT was involved in a decision regarding whether or not to commence NIV, the NIV initiation rates varied between 23-94% (see Table 17).(7,125,127,128)

Failure of continuous positive airway pressure prior to transfer

Failure of NIV prior to transport was reported in six CPAP transfer studies (n=583). (7,125,126,128,129) In these studies, there were 42/583 (7%) CPAP failure prior to transfer, with failure rate before transfer ranging from 1-13% (see Table 18). The reasons for CPAP failure were reported in 33/42 cases, with the most common reason given being intolerance of NIV (n=11).

Table 18: Failure of non-invasive ventilation prior to transfer

Study ID	NIV failure before transport	Mode of ventilation during transfer	Reason or evidence of NIV failure	Details
Baird-2009	1/32(3%) ¹	Spontaneously breathing room air	Intolerance of BiPAP mask	9-year-old boy with VP shunt problem and apnoea following opiates.
Bomont-2006	3/103(3%) ²	Intubated (3) ³	Poor arterial blood gas analysis & high FiO ₂ (1) ⁴ Poor arterial blood gas analysis & premature (1) ⁴	Patient 1: transferred age 95days (corrected GA 48 weeks) weight 3.12kg CPAP 7cm. Working diagnosis cardiac failure, congenital heart disease. Arterial pH 7.4, PaCO ₂ 7.1 FiO ₂ 80% ⁴ Patient 2: transferred on day of birth, GA 28 ⁺⁵ weight 1.03kg CPAP 5cm. Working diagnosis prematurity, RDS. Arterial pH 7.13, PaCO ₂ 10.1 FiO ₂ 40% ⁴ Patient 3: Infant with congenital heart disease. Intubated and ventilated by referring facility.
Fleming-2012	3/54(6%)	ND	ND	ND
Jani-2014	6/50(1%)	Intubated	Poor blood gas analysis (2) ⁵ ; Increasing respiratory distress (1)	pCO ₂ >55mmHg (2) ⁵ No reasons documented in 3 patients
Millan-2017	16/124(13%) ⁶	Intubated (6) O ₂ /nebulizer (10)	Lack of improvement (6); Poor tolerance of NIV (6); Interface size inappropriate (4)	ND
Murray-2008	13/220(6%)	Intubated	Apnoea on CPAP (3); increasing respiratory distress (4); failure to tolerate CPAP (4)	No reasons documented in 2 patients
TOTAL	42/583(7%)			

NIV, non-invasive ventilation; VP, ventriculo-peritoneal; BiPAP, Bi-level CPAP; FiO₂, fractional inspired oxygen; GA, gestational age; Pa O₂, partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide; ND, not documented; CPAP, continuous positive airway pressure.

¹ 9/32 patients were already on long term NIV (>1 month) prior to transport

² 2 failed CPAP in doctor-nurse team and 1 failed in nurse-led team

³ Sufficient details for reason to be determined for 2 of 3 CPAP failures

⁴ Unclear if this was bedside or laboratory blood gas analysis

⁵ Unclear if this was arterial, venous or capillary blood sampling and whether bedside or laboratory blood gas analysis

⁶ From data in Figure 1 Flow chart showing the stabilization measures applied by the retrieval team before transport.

Team composition

Details of the health professionals involved in the transfers was given in six studies (see Table 5).(7,125–129) Only two specifically mention the paramedic component: Baird et al.(125) report that 55% of transports were done by a team of two paramedics, and Jani et al.(128) describe paramedics as being part of the PICU transport team.

All six studies (7,125–129) describe using doctors as part of the transport team. In some studies, doctors took part in all transports (7,127–129), whereas other studies had doctors only for some transports.(125,126) Overall, where reported, a doctor accompanied 508/541 (94%) of patients transferred on NIV. The grade of the doctor involved in the transport was reported in five studies, as follows: paediatrician (129); transport-fellow (125,127) and 'advanced trainee' (7,128).

One study reported that 16% of NIV transfers had been done by a nurse-led team, with very specific criteria outlined for nurse-led transports.(126)

Transport mode, distance and duration

In three studies, NIV patients were all transported by road (125,126,129); the remaining five studies (7,8,127,128,130) were all conducted in Australia (see Table 19). The rate of road transport in the Australian studies ranged between 48-91%, with the remainder transported by either fixed-wing (5-14%) or rotor-wing aircraft (4-38%).

Distance was reported in four studies (8,127,128,130)), with the average distance (mean or median) ranging between 18-150 km. Duration of transport was reported in six studies (7,125–127,129,130) with average duration (mean or median) ranging between 34-72 minutes.

Table 19: Transport details

Study ID	Location	Unit or regional retrieval team (URT/RRT)	Team composition	Transport				
				Mode			Distance (km) Mean(\pm SD) ¹ Median (\pm Range) ²	Duration (mins) Mean (SD) ¹ Median (Range) ²
				Road	Air			
					FW	RW		
Baird-2009 (N=31)	New York State, USA	URT	2 x PM 17/31 (55%) 2 x PM + Transport Fellow 14/31(45%)	31(100%)	0	0	ND	56 (82) ¹
Bomont-2006 (N=100)	Cambridge & East of England, UK	RRT	84 Doctor + Nurse 16 Nurse-led	100(100%) ³	0	0	ND	60.3 (5.8) ¹
Fleming-2012 (N=51)	Victoria, Australia	RRT	Neonatal transport nurse + Transport Fellow	44(86%)	5(10%)	2(4%)	62 ¹	57 (51) ¹
Jani-2014 (N=44)⁴	New South Wales, Australia	RRT	Doctor (advanced trainee) + Transport nurse	24 (48%),	7(14%)	19 (38%)	150 ²	ND
Millan-2017 (N=108)	Catalonia, Spain	RRT	Paediatrician, Nurse + PM	108(100%)	0	0	ND	35 (20-65) ²
Murray-2008 (N=207)⁵	Victoria, Australia	RRT	Doctor (advanced trainee) + Transport nurse	190(86%)	10(5%)	20(9%)	ND	34 (5-110) ²
Resnick-2010 (N=167)	W Australia, Australia	RRT	ND	152(91%)	15(9%)	0	18 (1-2846) ^{2,6}	ND
Schlapbach-2014 (N=150)	Queensland, Australia	URT	ND	117 (78%)	8(5%),	25(17%)	96 (25-744) ¹	72 (6-228) ¹

URT, unit retrieval team; RRT, regional retrieval team; FW, fixed-wing aircraft; RW, rotor-wing aircraft; PM, paramedic; ND, not documented;

¹Mean, standard deviation

²Median, interquartile range

³Not specified but assumed to be all road transports due to local geography

⁴Data reported for all 50 transports in the study, with 44 transferred on CPAP

⁵Data reported for all 220 transports, with 207 transferred on CPAP

⁶Reported for all 369 patients, including those transferred on CPAP (n=167), IPPV (n=107) and cot oxygen (n=95)

CHAPTER 6: DISCUSSION

Introduction

To the authors' knowledge, this is the first systematised review of the literature on NIV transport in children. Systematic review data exists for NIV use in hospitalised children, particularly for those in intensive care settings; however, no such review data exists for NIV use in children during transport.

This review included eight observational studies of NIV use in children during transport: seven studies (n=708) evaluated CPAP during transfer and one study (n=150) reported on HFNC use during transport. There were no RCT, QRCT or NRSI identified, and thus all the evidence reported in this review is based on low-reliability research.

Intubation or Escalation of Ventilation during Transfer

Transportation of children on NIV appears safe, with only 3/858 (0.4%) patients requiring either intubation (1/708; 0.1%; CPAP studies) or escalation of mode of ventilation (2/150; 1%; HFNC study) during NIV transfer. High-quality trial data for children is not available for comparison, but these findings are in keeping with reported rates of intubation of adult patients on NIV during transportation 0-3.2%.^(117,135)

The intubation rate of 0.1% during transfer on CPAP and 1% escalation to CPAP during transfer on HFNC should not be interpreted to mean that HFNC is ten times riskier during transfer, as other factors are likely to account for this difference. For example, the perceived ease of application of HFNC compared with CPAP, and the reduced need for sedation, may result in HFNC being started in cases that may have benefited from CPAP earlier. If they are then transferred before it becomes apparent that HFNC is not sufficient respiratory support, this could explain the increased escalation during transportation.

It is not possible to comment on the relative safety or effectiveness of B_LCPAP during transfer as there were insufficient patient numbers and details reported.

Intubation or Escalation of Ventilation after Transfer

In the 24 hours following transfer, 63/650 (13%) of children transferred on NIV were intubated. Significantly more children transported on CPAP were intubated within 24 hours 60/500 (12%) compared with HFNC 3/150 (2%), p=0.00003.

Again, there is a lack of high-quality trial data for children transported on NIV for comparison. Previous studies have described a need for immediate intubation on arrival at destination in 11% of adults (136) and 13% of paediatric patients.(137) Systematic review and meta-analysis data has found that CPAP administration during transport of adults reduced the risk of subsequent intubation (OR 0.32, 95% Credible Interval 0.17 to 0.62) compared with standard care (9), but no such evidence exists for NIV use in children during transport.

The higher rate of intubation in children transferred on CPAP compared with HFNC, should not be interpreted to mean that HFNC itself results in a six times reduction in the likelihood of intubation in the 24 hours after transport. As HFNC is a newer, less 'tried and tested' therapy, it may be that HFNC was used in less sick children. Whereas children with more obvious respiratory difficulty may have been started on CPAP prior to transfer, and subsequently the sicker CPAP group, required a higher rate of intubation. A lack of reporting of severity of illness measures and/or indications for NIV, in the inclusion and exclusion criteria of included studies, means that this possibility is open to speculation but cannot be confirmed or refuted.

With regard to available information on intubation following transfer in the included studies, most studies either specified the number of patients intubated within 24 hours, or this number could be calculated from the data given. For some studies, the reported end point was at 24 hours; other studies continued their follow-up beyond 24 hours or did not specify the duration of follow-up. This variation in follow-up cut-off makes it difficult to compare studies and impossible to know the true rate of overall intubation following NIV transportation in these studies.

It was unclear in most studies whether the patients were being transferred from lower to higher levels of care (up-transfer), being returned to lower levels of care (down-transfer), or a combination of both. The relative proportions of up- and down-transfers would influence the anticipated severity of illness, both during and after transfer. As this baseline cannot be discerned, this adds to the difficulty in comparing intubation and AE rates between these studies. Hence, it is also problematic to generalise the findings of this review.

In this area of research, intubation following transfer is generally being used as a proxy measure for 'failure of NIV'. The implication presumably is that significant worsening of respiratory failure after transfer means that the patient should not have been transferred on NIV in the first place. However, it is not as clear-cut as this.

One study (7) reported that 11/32 (34%) of infants transferred on NIV were intubated for surgery following arrival at destination. However, few other studies mentioned any information on the number of patients intubated for procedures such as surgery after arrival. This would not necessarily be considered a failure of NIV, and so it is important to know the proportion of patients being intubated for procedures or surgery and thus to differentiate between those who deteriorated and those who were intubated for other reasons.

Critically ill patients transferred to a higher level of care are often being transferred because deterioration is expected, the exceptions being transfers done for consultation, surgery or procedures unavailable at the referring facility. It is widely accepted that intubation should take place under controlled circumstances and by experts who have recourse to a spectrum of back-up equipment, skills and facilities should anything go wrong. Therefore, not intubating prior to (or during) transfer is likely to be in the patient's best interests, as long as those who need earlier IPPV are recognised. Thus, being intubated after arrival may not necessarily be a signal of failure but rather of success: the riskiest procedure happened in the right place.

It is not possible to comment on the relative safety or effectiveness of B_iCPAP after transfer as insufficient patient numbers and details were reported.

Adverse Events during Transfer

Adverse event rates

Adverse events, where reported, were found to occur in between 2-4% of NIV transports, with use of BVM in 8/334 (2%), desaturation episodes in 9/290 (3%), apnoea in 11/290 (4%) and administration of CPR in 0/290 (0%) cases being described. These results were extrapolated from two studies (125,126) that reported these AEs directly combined with studies that made statement to the effect of no AEs having occurred during transport.

These findings are in keeping with the 4% preventable physiological AE rate reported by Britto et al. for transfers done by a specialised paediatric RT.(138) But this rate is well below the reported range of 33-75% AEs during emergency transport of adults and children.(27,135–137) This raises the suspicion that the included studies may not have captured or reported AEs adequately.

Poor reporting of adverse events

Evaluating evidence on this topic was significantly hampered by the fact that few studies specifically mentioned, or gave sufficient details of, AEs experienced during the transport phase. This was true even of the one prospective observational study (129) which, similar to several other studies, made a generic statement, 'No other complications results from NIV/CPAP in our subjects.'

These kinds of statement are of little use when attempting to appraise evidence on the safety of NIV. What is needed are unambiguous details as to the presence or absence of key AEs that might reasonably be expected to occur. This includes episodes of desaturation, bradycardia, apnoea or the need for interventions such as suctioning, BVM ventilation or CPR. This level of detail was reported only in two studies (125,126), but the wording was still unclear and containing statements such as, 'Airway suctioning and/or use of BVM during transport were performed on 8/31 transports because of episodes of desaturation, occasionally with bradycardia'.(125)

Lack of details available in database information

The ill-defined reporting of AEs is likely to be related to a paucity of AE details in the databases being used to inform the studies. This lack of specific information is a serious limitation in the interpretation of the occurrence of AEs and, hence, of safety during transport of children on NIV. As such, one of the recommendations stemming from this study is the setting up detailed registries for patients transferred on NIV. Alternatively, where a current transport database exists, the recommendation would be to expand the AE section to require confirmation of the presence or absence of key AEs during transport.

Secondary Safety and Effectiveness Outcomes

Difficulties evaluating secondary outcomes

Evidence of clinical improvement after commencing NIV or stability of vital signs of patients transported on NIV, was even less well reported than were AEs during transport.

Accurate vital signs measurement in neonates and children can be difficult, even in stable, controlled environments such as hospitals (139,140) and this would be expected to be even more challenging in transport settings. The problems that could interfere with manual

measurement or electronic monitoring of clinical improvement and stability parameters include motion artefact, vibration, and upset child due to noisy environment and separation from parent or carer.

Clinical parameters in included studies were measured at discrete time-points for individual patients and then averaged for the entire group. In such small studies, this does not give a useful indication of genuine change in these factors. It would be more helpful to know how the trend of each parameter varied per patient and whether, in overall terms, more or fewer patients showed signs of improving, worsening or no change during transfer on NIV.

Vital signs during transfer

Only two studies (125,128) described HR and RR of patients during transport on NIV. Both studies found that these parameters did not alter significantly between two time-points in transfer. Just one study (125) reported on SaO₂ during transfer and found that this did not change significantly from start to end of transfer. Surprisingly, no studies described the effect of NIV on work of breathing before, during or after transfer.

Research on prediction of failure of NIV in children has shown that, whilst no single parameter can accurately identify patients who will go on to require IPPV, clinical signs are useful in the recognition of such children.(141–144) The Paediatric Risk of Mortality (PRISM) score, Type 1 ARF and lack of reduction of RR following initiation of NIV were found to be independently associated with CPAP failure.(142) Non-responders to HFNC were differentiated from responders by lack of reduction in HR or RR within 60 minutes of starting treatment.(143) The findings of this review with regards to HR, RR and SaO₂ during transfer, suggest no change in these parameters during transport. This may in part be explained by the small numbers and the fact that transport durations were relatively short (on average 34-72 minutes), in comparison to the NIV duration in most studies.

Fractional inspired oxygen during transfer

Three studies(7,8,127) in this review found a significantly lower FiO₂ ($p < 0.001$, in all three studies) on arrival at destination compared with at start of transfer. These findings are in keeping with evidence that a lower FiO₂ is an indicator of NIV success.

Non-invasive ventilation studies have previously suggested that a persistently high FiO₂ is linked with NIV failure.(144,145) An FiO₂ over 80% one hour after commencing CPAP was predictive of NIV failure (sensitivity 56%; specificity 83%) in children with ARF.(145) An FiO₂

over 50% two hours after initiating NIV was a predictive factor for failure of HFNC in children with moderate to severe respiratory distress.(144)

Two studies (7,128) in this review analysed FiO_2 separately for patients who were successfully transferred on NIV compared with those who failed. Jani et al.(128) described a significantly higher FiO_2 at arrival ($p < 0.05$) in NIV failures and Resnick et al.(8) found a significantly higher FiO_2 at the start ($p < 0.0001$) and end of transport ($p < 0.001$) in 107 infants who were transported intubated, compared to 22 infants who went on to be intubated in the first 24 hours, and 145 infants transferred successfully on CPAP. Murray et al.(7) reported that 9 (4%) of the patients transferred on NIV had rising FiO_2 during transfer and 4 (44%) of these patients went on to be intubated within 24 hours of arrival at destination.

Transcutaneous carbon dioxide during transfer

Transcutaneous CO_2 was reported as not changing from start to end of transfer in two studies (7,127). One of these studies described a 20% intubation rate, within 24 hours of transfer, in patients in whom tCO_2 rose by more than 7mmHg during transfer.(7) These findings are in keeping with accepted knowledge that rising CO_2 levels are associated with worsening respiratory failure and increased likelihood of need for IPPV.(2,3,141)

Of course, signs of clinical improvement and ventilatory parameters would need to be placed in the context of the NIV used, interface selected and the NIV protocol and settings used during transport. It was disappointing that so little detail was provided on the latter in the studies. Once again, the impression one is left with is that the studies reported only what was available in their databases, leaving significant gaps in terms of information needed to evaluate safety and effectiveness of NIV during transport.

Mortality during and after transfer

Mortality was not adequately reported as an outcome in the included studies. This is unfortunate because concerns have been raised that inappropriate use of NIV could potentially delay necessary IPPV and thus be harmful to patients. This is particularly a concern with HFNC, which is a newer and less proven treatment but one that has become popular in intensive care and emergency settings. Hutchings et al. provide anecdotal evidence of inappropriate HFNC use leading to emergency intubation with a need to convert immediately to high pressure ventilation and even high-frequency oscillatory ventilation.(51) An adult ICU study found that those receiving IPPV after more than 48 hours of HFNC,

compared to earlier intubation, had significantly worse outcomes for extubation success, ventilator weaning and mortality.(87)

Strengths and Limitations

Strengths

The strengths of this review include the rigorous systematic methodology employed, with comprehensive search of major research databases and trials registries and the use of independent dual reviewers during selection and quality assessment of studies for inclusion. Furthermore, an adapted QA tool for observational studies of NIV use in transport, has been developed, based on an established QA tool. There was a high level of inter-rater agreement for assessment for the quality of studies using the adapted tool.

To the author's knowledge, this is the first systematised review of the literature on NIV transport in children, and despite the limitation of the quality of evidence available, a thorough, methodical and rational appraisal has been made of the research evidence to date.

Limitations

The search was limited to articles published in the English language, this may have resulted in some relevant studies being missed. The grey literature was not actively searched and beyond searching the reference lists of included studies, no other hand-searching was done. Again this could have resulted in non-identification of eligible studies. This study did not address the question of NIV use during primary emergency transports (i.e. from home or scene to hospital) therefore no comment can be made on appropriateness of NIV for this purpose.

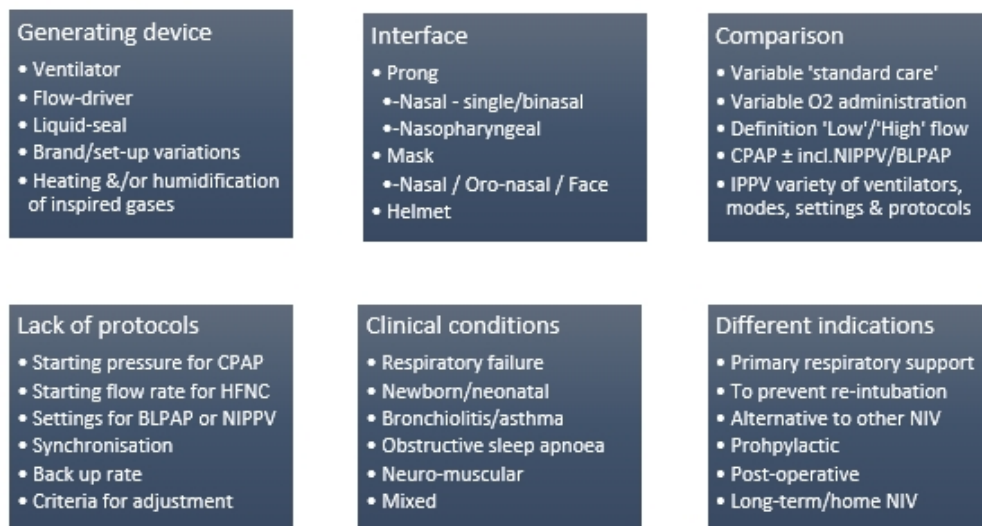
No RCT, QRCT or NRSI evidence regarding NIV use in children during transport was identified for this review. The evidence included comes from observational studies, mostly with retrospective record review design, with some studies comparing outcomes in children managed before and after introduction of NIV. These types of studies are capable of providing only low levels of evidence. Quality evaluation of studies proved problematic as the available information precluded use of standard tools. A custom-made QA tool was adapted for this purpose, but a weakness of this study is that this tool has not been formally validated.

The data provided by the studies included in this review was almost universally extracted from pre-existing transport or ICU databases. Reliance on such database material runs the

risk of study authors describing what they were able to find, rather than what would be most useful to know. There is also a tendency to make sub-group comparison, such as NIV failure versus success, with group sizes that are too small to allow meaningful conclusions to be drawn.

Evaluating the evidence regarding NIV use in children is further hampered by the sheer variation in important aspects of NIV equipment, patient selection and NIV protocols, not to mention the variety of comparisons used (see Figure 9).⁸ This diversity is further complicated by the patchy nature of reporting of important variables such as NIV settings used; clinical parameters before, during and after transport; and length of follow-up period.

Figure 9: Variable factors in NIV research in children



These variations between studies are overcome to some degree when there is a large enough body of high-quality trial-based research to permit meaningful meta-analysis. This is the current situation for hospital-based neonatal NIV research, but we are very far from reaching this point in paediatric or neonatal transport NIV research.

⁸ This figure was created by Baljit Cheema for this dissertation.

CHAPTER 7: IMPLICATIONS, CONCLUSION AND RECOMMENDATIONS

Clinical Implications

Safety and effectiveness

In the past few decades, paediatric and neonatal hospital practice has shifted towards use of NIV in an attempt to avoid the risks associated with intubation and invasive ventilation.(1,2,6,32) The parallel shift to NIV use in the pre-hospital setting, has been slower. This study suggests that NIV use in children during transport is safe, with a 0.4% escalation and AE rates of 2-4% during transport. Unfortunately, the jump to advocating increased use of NIV during transportation of children cannot be made as the findings are based on low-quality evidence.

Timing of referral

It is generally accepted that non-invasive ventilation is not appropriate for use in children with severe respiratory distress. (2,3,92) Therefore, if a child is to be transferred on NIV, referrals may need to be made earlier in the course of respiratory illness. As discussed, one of the benefits of transfer on NIV is that intubation, if needed, would occur at the higher level of care with greater skills and resources. However, a paradigm shift towards earlier referral could result in an increased burden on PICU and HCU beds. This is because some of the transferred patients would previously have remained at referral centres, with only those deteriorating sufficiently to require intubation being transferred.

Research Implications

Ethical considerations

Given how widespread NIV use has become in children in clinical settings (1,2,6,32), there are some who question whether it is even ethical to conduct future trials with comparison groups where no NIV is given.(2) This is a conundrum that those wishing to conduct pre-hospital NIV research may face imminently. Traditional oxygen administration as an alternative to NIV, in pre-hospital (or hospital) NIV trials, may soon be considered an unethical option. Whether clinical equipoise still exists is a matter that clinicians and researchers will need to decide on in the near future.

Practical aspects of conducting research on this topic

In general, large-scale paediatric multi-centre randomised-controlled trials of sufficient power to detect meaningful differences are difficult to conduct, even when they involve

specialist paediatric staff working in established units. Attempting to conduct such high-quality rigorous trials for NIV use in children in the pre-hospital setting would be a daunting, undertaking and perhaps impossible.

Numerous local variations and considerations would need to be taken into account, such as geography, transport infrastructure, levels of health-care and health-system referral configuration. Additionally, factors relating to EMS structure and operation itself could influence results, such as access to specialised or non-specialised RT, unit-based or regional RT, team composition, vehicle configuration, available equipment, level of training and access to senior medical support during transfer. Ultimately, it may prove impossible to conduct high-quality trials to determine the efficacy of NIV use in children during transport.

Feasibility of study designs for this topic

Observational studies appear to be the predominant study type in this field and as outlined above, it is likely that they will continue to be the most pragmatic and feasible study design for research on this topic. In future, it would be preferable if researchers were to conduct methodologically rigorous studies with prospective data collection to include many of the clinical parameters which are currently missing in the published literature.

Recommendations are given below on how observational studies of NIV use in children during transport could be strengthened to provide more reliable and more comparable information.

Quality and completeness of reporting

In order to improve the comparability of studies evaluating the use of NIV in children during transport, sufficient detail needs to be provided on the study methodology. This should be done in a standardised format to permit assessment of the internal and external validity.

In addition to a comprehensive description of the methodology used, it would be very helpful if there was greater standardisation of the essential outcomes reported in observational studies. As discussed earlier, detailed registries or expanded transport databases, will help improve the comparability of outcomes of NIV use during transport of children.

It is important that outcomes are actively looked for and prospectively recorded, even if to note that these events did not occur. For example, active surveillance for AEs with recording of presence or absence of pre-defined events such as apnoea, bradycardia, desaturation, suctioning, etc. would be very helpful.

The delineation and explanation of the time-frames involved is also essential to permit interpretation and comparison of the results of observational studies of NIV use in children during transport. For example, with regard to the duration of follow-up for intubation or air leak after NIV transport, it is important to know if follow-up was for a limited cut-off period after arrival or was continued until discharge or death. Transparency of methods and standardisation of reporting will assist greatly with evaluation of evidence in this field.

Standards already exist for reporting of RCT studies (146) and systematic reviews and meta-analysis(147) and a range of observational study types (123). This study proposes a minimum data-set to be reported in observational studies researching the use of NIV during transport of children, including details of: patient variables, transport details, NIV equipment, interfaces and protocols and clinical outcomes – see Table 20.⁹ This minimum data-set was developed by the primary researcher during the study, by consideration of the missing information and elements that if included, would have permitted greater ease of comparison between studies of NIV during transport of children.

Table 20: Minimum data-set to be reported in studies on paediatric non-invasive ventilation during transport

Variable	Minimum details to report
Patient details	
Age	<p>Neonatal studies</p> <ul style="list-style-type: none"> • Gestational age PLUS At time of transport: • Age in hours if majority less than 1 day • Age in day if majority > 1-28 days <p>Infants & children</p> <ul style="list-style-type: none"> • Age in months
Reason for starting NIV (Presentation or diagnosis)	<p>Presenting symptom – e.g. acute respiratory distress, neuromuscular weakness, presumed sepsis etc. This is often more realistic than definitive diagnosis for emergency transfers</p> <p>Definitive diagnosis may be available for non-acute presentations</p>
Inclusion & exclusion criteria	Explicit pre-determined inclusion and exclusion criteria must be reported
Chronic NIV	The number of patients already on long-term NIV at home/facility e.g. >1month

⁹ Note that the table was developed by Baljit Cheema for this dissertation.

Transfer details	
Type of EMS team effecting transfer	<p>Non-specialised vs. specialised</p> <p>Unit-based RT vs Regional RT</p> <p>Scope of work of RT: neonatal only, paediatric & neonatal or paediatric, neonatal and adult transfers</p>
Team composition	<p>Number of staff and type:</p> <p>Paramedic, respiratory technician, nurse, specialised critical-care or transport nurse, doctor (seniority: trainee, fellow, specialist)</p>
Mode of transport (%)	<p>Road</p> <p>Air: fixed versus rotary wing</p>
Distance (km)	Measure of central tendency and spread as appropriate to the data
Duration (min)	<p>Measure of central tendency and spread as appropriate to the data</p> <p>Standardise duration e.g. from time of entering the referring unit/ward until time of entering receiving unit</p>
Up or down transfer	<p>Percentage being taken to higher/lower level of care</p> <p>Analyse separately, as required.</p>
NIV details	
Availability of NIV in referring facilities	Give indication of availability of NIV and levels of skill at referring facilities e.g. 24-hour on site specialist or specialty trainee versus general practitioner or medical officer
NIV started by whom	Referring facility or retrieval team
NIV generating device(s)	Details of brand, model, manufacturer
Power supply	Does the device have battery power? If not how was the patient transferred from unit to vehicle and vice versa at receiving unit
Medical gas supply	Does the vehicle have medical air? If not, how was FiO ₂ titrated? e.g. air compressor in NIV generating device
NIV interface(s)	Details of brand, model, manufacturer
NIV mode	Details of mode(s) used using standardised terminology as per NIV device/model
NIV settings & protocol	<p>Starting pressure or flow rate</p> <p>Protocol for adjusting pressure or flow rate</p> <p>Use of sedation</p> <p>Duration of NIV prior to departure</p>
NIV for transport failures	<p>Those in whom NIV was started, specifically by the RT, but who were not transported on NIV. Report on duration of NIV trial, reason for failure and what form of ventilation/oxygenation, these patients were transported if not on NIV.</p> <p>Report separately those in whom NIV was started by referring facility but who subsequently were not transferred on NIV.</p>
Clinical details	

Clinical parameters at referring facility	HR, RR, WOB, SaO ₂ , FiO ₂ , measures of CO ₂ e.g. tCO ₂ , ETCO ₂ , blood gas pH/PaCO ₂ On RT arrival and at time of departure
Clinical parameters during transport	HR, RR, WOB, SaO ₂ , FiO ₂ , measures of CO ₂ e.g. tCO ₂ , ETCO ₂ , blood gas pH/PaCO ₂ Reported for regular intervals during transfer e.g. every 10minute
Clinical parameters on arrival at receiving unit	HR, RR, WOB, SaO ₂ , FiO ₂ , measures of CO ₂ e.g. tCO ₂ , ETCO ₂ , blood gas pH/PaCO ₂
Adverse events during transfer	Apnoea, desaturation, bradycardia, tachycardia Need for BVM or CPR Need for suctioning Need to reposition interface Interface leak compromising NIV Need for sedation Air leak identified during transfer
Escalation of ventilation during transport	Need for intubation Escalation of HFNC to CPAP or B _i PAP Give timing and reasons Give details of outcome of these patients to discharge
Escalation of ventilation after transport	Need for intubation Escalation of HFNC to CPAP or BLPAP Give reasons for escalation – failures (a priori defined) and non-failures e.g. for surgery or procedure Give timing of escalation e.g. <2hours; 2-24hours; >24hours to discharge Give details of outcome of these patients to discharge
NIV linked adverse events after transfer	Air leaks Local pressure effects Inappropriate delay to intubation and IPPV
Duration of follow up	Explain duration of follow up and how follow up was done e.g. daily record review, telephone, database information etc. If follow up was done differently for different variable – explain details e.g. re-intubation from record review, days in ICU from hospital database etc.
Survival to discharge	Report on the numbers of patients transferred on NIV surviving to discharge

Conclusion

The evidence in this review comes from eight observational studies, as no RCT, QRCT or NRSI studies were identified in the search. This study provides the first systematised review on this topic, and the findings suggest that NIV use in children during transport is likely to be safe. From the low-reliability evidence available, it was calculated that NIV use in children during transport would result in a 0.4% rate of intubation or escalation during transport and an in-transport AE rate of 2-4%. There was insufficient evidence to comment on clinical effectiveness of NIV during transfer. Following transfer, 13% of patients were intubated within 24 hours.

Recommendations

This results of this review suggest that NIV during inter-facility transport of children may be safe, but further research is needed on this topic before firm recommendations can be made.

Ethical and practical considerations make it unlikely that there will ever be large, high-quality multi-centre RCT studies conducted on this topic. The alternative would be for researchers to undertake prospective observational studies, using sound methodologies and comprehensive, standardised reporting.

A recommended minimum data set for standardised reporting of observational studies, of NIV use in children during transport, is suggested. It is recommended that transport databases and registries, are expanded to include details of NIV equipment, interfaces and protocols, as well as indicators of clinical condition and the presence or absence of pre-specified AEs during transport.

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APPENDICES

Appendix A: Assessment of Quality of Evidence

Quality assessment tools

The answers obtained from systematic reviews are only as good as the evidence they draw upon. It is therefore important that studies included in systematic reviews should be systematically appraised for quality.(148)

Levels of evidence

Account must be taken of the inherent risk of bias involved in different study types. More rigorous study designs involve active efforts to control for sources of bias and confounding factors, through randomisation of participants to interventions or treatments. However, it may be difficult or impossible to undertake randomised trials in certain clinical settings and observational studies offer alternative study formats under these circumstances.

The Oxford Centre for Evidence Based Medicine (OCEBM) separates evidence into a hierarchy of five levels depending on the type of research question being addressed, with systematic reviews of RCT studies most commonly constituting level 1 evidence.(149) For research into the effect of interventions, the OCEBM categorises non-controlled observational studies as being capable of providing level 4 evidence, which is the weakest form of study-based evidence; only 'mechanistic reasoning' qualifies for a lower rating (level 5).(149) Another classification, by Akobeng rates systematic reviews as the highest level of evidence followed by RCTs, cohort studies, case-controlled studies, case-series, case reports and opinion forming the lowest level of evidence.(150)

QA tools for randomised study design

Tools appropriate for assessing the quality of evidence from this study design include the Cochrane Risk of Bias tool(120), the Jadad scale(151) and the Schulz system.(152)

QA tools for non-randomised studies of interventions

Several QA tools have been developed for specifically for non-randomised studies of interventions (NRSI) design. These include the Newcastle-Ottawa Scale (NOS)(153) and the

new Cochrane Collaboration tool: Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I).(121,122)

QA tools for observational studies

RCT evidence does not exist for many health topics. In the face of lack of RCT evidence in certain fields of healthcare, there is an increasing acceptance of the value observational study designs.(154–156) The Enhancing the QUALity and Transparency Of health Research (EQUATOR) network has a library of QA tools and resources for a variety of study types.(157) This site has links to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) tool for QA of cohort, case-control and cross-sectional studies.(123) There is also a QA tool for individual case reports: The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.(158,159) However, there is no suggested QA tool for case-series studies.

Moga et al. conducted a systematic search for QA tools for case-series. They found 36 studies reporting QA checklists for observational studies in healthcare: 10 created specifically for case-series studies and 26 which assessed this study design as well as other designs.(124) They collated criteria from five of these studies that met their quality inclusion criteria into a 30-item tool. A four-round Delphi process was conducted and consensus reached on 18 items, which form a new QA tool for case-series. This tool was then validated by three independent reviewers on 13 case-series studies.(124)

The authors are clear in their discussion and conclusion that the tool they have developed is a guide and should be modified by systematic reviewers according to the criteria most relevant for their field. They also stipulate that whilst they did not incorporate a score or grading system, future users of this QA tool may wish to stipulate cut-offs for distinguishing low- from high-quality studies.(124)

QA tool adapted for this study

The Moga 18-item tool (Appendix B) was adapted for use in this study into a 20-item generic observational study QA tool for use in studies of NIV during transport (Appendix C). The process undertaken in the adaptation thereof is described further in Chapter 4: Methodology.

Appendix B: Quality Appraisal Tool for Case-Series Studies

Criterion number	Criterion
1	Is the hypothesis/aim/objective of the study stated in the abstract, introduction, or methods section?
2	Are the characteristics of the patients included in the study clearly described
3*	Were the case series collected in more than one centre?
4	Are the eligibility criteria (inclusion and exclusion criteria) explicit and appropriate?
5	Were patients recruited consecutively?
6*	Did patients enter the study at a similar point in the disease?
7#	Did the authors describe the intervention?
8#	In addition to intervention, did the patients receive any co-interventions?
9#	Was loss to follow-up reported?
10	Are outcomes (primary, secondary) clearly defined in the introduction or methodology section?
11*	Did the authors use accurate (standard, valid, reliable) objective methods to measure the outcomes?
12*	Were outcomes assessed before and after intervention?
13*	Was the length of follow-up clearly described/reported?
14	Were the statistical tests used to assess the primary outcomes appropriate?
15	Does the study provide estimates of the random variability in the data for the primary outcomes (e.g. standard error, standard deviation, confidence intervals)?
16#	Are adverse events that may be a consequence of the intervention reported?
17	Are the conclusions of the study supported by results?
18#	Is there a competing interest statement about the type and source of support received for the study or about the relationship of the author(s) or other contributors with the manufacturer of the technology?

Source: Extracted from Moga C, Guo B, Schopflocher D, Harstall C. *Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique*. Edmonton AB: Institute of Health Economics. 2012.

*Criteria which were deleted in the adapted QA tool

Criteria which were modified in the adapted QA tool

Appendix C: Adapted Quality Appraisal Tool for Observational Studies of NIV in Transport

Criterion number	Criterion	Yes 1	PR 0.5	No 0
1	Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section?			
2	Are the characteristics of the participants included in the study described?			
3	Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?			
4	Were participants recruited consecutively?			
5*	Was the make-up of the transport team adequately described?			
6*	Were transport distances &/or durations described?			
7*	Were modes of transport described? (i.e. road, air: rotary/fixed wing)			
8*	Was the method of NIV generation clearly described in the study? (Device details, manufacturer, model etc.)			
9*	Was the type of NIV interface used described? (nasal/NP prongs, mask, helmet etc.)			
10*	Is there adequate description of the NIV protocols used? (indications, contraindications, pressure/flow etc.)			
11#	Were additional interventions (co- interventions) clearly reported in the study?			
12	Are the outcome measures clearly defined in the introduction or methods section?			
13#	Were relevant outcomes appropriately measured with objective and/or subjective methods? (Even if not defined in intro/methods)			
14#	Are adverse events reported?			
15#	Was there any follow up after the immediate transport period?			
16*	No new results are reported in the discussion section			
17	Were the statistical tests used to assess the relevant outcomes appropriate?			
18	Does the study provide estimates of the random variability in the data analysis of relevant outcomes?			
19	Are the conclusions of this study supported by the results?			
20#	Are both competing interest and source of support for the study reported?			

PR, partially reported; CD, cannot determine; NA, not applicable; NR, not reported. **SCORING:** 1 point if adequately reported; 0.5 points if partially reported and 0 points if not reported.

*New criteria added in the adapted QA tool

#Modified criteria added in the adapted QA tool

Appendix D: Details of Studies Used in Clinical Effectiveness of Non-Invasive Ventilation in Neonates Section of Literature Review

Five systematic review and meta-analysis studies (41,45,67,90,91) were used to provide the information collated into Tables 9-11 of the literature review for this dissertation. The table below contains details of the study types, participants, interventions, comparisons and primary and secondary outcomes for these five reviews. This information has been directly copy-pasted from the original reviews, or has been extracted with minor editing, to give coherence and consistency to the table.

	Subramaniam(41)	Ferguson(90)	Lemyre(91)	Wilkinson(45)	Kotecha(67)
Study types	RCT or QRCT	RCT	RCT or QRCT (excluding crossover trials)	RCT or QRCT (including crossover trials)	RCT or QRCT
Participants	<32 weeks GA or <1500g	intubated preterm infants <37 weeks GA	Newly born <6hr old and <37 weeks GA	1. Preterm infants (< 37 weeks' gestational age) receiving respiratory support after birth, either prophylactically or for respiratory distress syndrome, without a prior period of intermittent positive pressure ventilation (IPPV). 2. Preterm infants (< 37 weeks' gestational age) receiving respiratory support following a period of intermittent positive pressure ventilation (IPPV).	<37 weeks GA
Interventions	Prophylactic nasal CPAP starting within 5 to 15 minutes of life regardless of the respiratory status of the infant compared with other forms of treatment.	CPAP, NIPPV and HFNC	NIPPV provided by a ventilator or a bilevel device and administered via the nasal route through short nasal prongs or nasopharyngeal tubes	HFNC oxygen = delivery of oxygen or blended oxygen and air via nasal cannulae at gas flow rates greater than 1 L/min.	For the purposes of this review, HFNC was defined as heated humidified flows in excess of 2 L/min (low flows are defined as <2 L/min).
	Subramaniam(41)	Ferguson(90)	Lemyre(91)	Wilkinson(45)	Kotecha(67)

Comparisons	<p>1. CPAP started soon after birth compared to supportive care which may include supplemental oxygen delivered by head box or standard nasal cannula.</p> <p>2. CPAP compared to assisted ventilation with or without surfactant started within the first 15 minutes of life usually in the delivery room</p>	<p>CPAP v Head-box BuCPAP v Ventilator CPAP Variable flow v Ventilator generated CPAP BuCPAP v variable flow CPAP Lower vs Higher CPAP Pressure Binasal vs Single-Nasal Prongs Nasal Mask vs Short Binasal Prongs</p> <p>Nonsynchronized NIPPV vs Head-Box Oxygen Nonsynchronized NIPPV or BiPaP vs CPAP Nonsynchronized NIPPV or BiPaP vs CPAP HFNC vs CPAP Humidified vs Nonhumidified HFNC Comparison of Different HFNC Devices</p>	<p>NCPAP delivered by the same methods as above.</p>	<p>Alternative interventions included:</p> <ul style="list-style-type: none"> • Head box oxygen; • Low flow nasal cannulae (gas flow rates less than or equal to 1 L/min); • Nasal CPAP; • NIPPV; • HFNC using an alternative technique (e.g. humidified versus non-humidified, or different HFNC devices). 	<p>Other modes of NIV including nCPAP, and NIPPV or BiPAP</p>
Primary outcomes	<p>1. Failure of treatment as indicated by recurrent apnoea, hypoxia, hypercarbia (such as PaCO > 60 mmHg) and increasing oxygen requirement or the need for mechanical ventilation</p>	<p>The primary outcomes were (1) treatment failure (as defined in the studies), and/or (2) reintubation, both within 7days of extubation.</p>	<p>1. Respiratory failure: defined by respiratory acidosis, increased oxygen requirement, or apnea that was frequent or severe, leading to additional ventilatory support during the first week of life 2. Need for endotracheal tube (ETT) ventilation (intermittent positive pressure ventilation (IPPV) through an endotracheal tube)</p>	<ul style="list-style-type: none"> • Death (before hospital discharge) or chronic lung disease (as defined below); • Death; • Chronic lung disease. CLD was defined as a requirement for supplemental oxygen and/or respiratory support at 36 weeks' postmenstrual age (PMA) for infants born at less than 32 weeks' gestational age or at 28 days of age for infants born at 32 weeks' 	<p>Primary outcomes were failure of therapy to establish efficacy, and death, pulmonary air leaks, and nasal trauma to establish safety.</p> <p>Any definition of failure of therapy was</p>

	2. Rate of BPD; a) oxygen therapy at 28 days with or without an abnormal chest X-ray; b) oxygen therapy at 36 weeks' postmenstrual age 3. Mortality to latest follow-up 4. Combined outcome of BPD and mortality			gestational age or later. Note: data from studies that reported an outcome of 'CLD' or 'bronchopulmonary dysplasia' ('BPD') without an	considered, because there were differences in how various researchers defined it in trials.
	Subramaniam(41)	Ferguson(90)	Lemyre(91)	Wilkinson(45)	Kotecha(67)
Secondary outcomes	1. Use of surfactant 2. Pulmonary air leaks (pneumothorax, pneumomediastinum) 3. Local trauma (nasal injury, subglottic stenosis, laryngeal injury) 4. Feed intolerance (days to full feeds) 5. Rate of intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) 6. Necrotizing enterocolitis (proven by radiology or at surgery) 7. Rate of late onset systemic infection 8. Retinopathy of prematurity (ROP) Subramaniam(41) (cont)	N/A	Mortality (neonatal and before discharge) • Major neurodevelopmental disability (cerebral palsy, developmental delay (Bayley or Griffith assessment greater than two standard deviations (SDs) below the mean) or intellectual impairment (intelligence quotient (IQ) greater than two SDs below the mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification) • Chronic lung disease (oxygen therapy at 36 weeks' postmenstrual age) • Pneumothorax • Patent ductus arteriosus • IVH (all grades) (Papile 1978) • Severe IVH (grade III/IV) (Papile 1978)	Treatment failure • Intubation (or re-intubation) within 7 days of trial entry. Note: studies that reported intubation (or re-intubation) within a shorter period than 7 days (e.g. intubation < 72 hours) were included in the analysis of this outcome; • Treatment failure (as defined by the trial authors) within 7 days of trial entry. Note: studies that reported treatment failure within a shorter period than 7 days (e.g. treatment failure < 72 hours) were included in the analysis of this outcome; • Intubation at any time point following trial entry. Respiratory support:	Data on several secondary outcomes were collected, including respiratory outcomes (respiratory complications, mode, and length of respiratory support, bronchopulmonary dysplasia [BPD]), intraventricular hemorrhage (IVH), and other relevant neonatal outcomes (sepsis, necrotizing enterocolitis [NEC], Kotecha(67) (cont)
Secondary outcomes (cont)	9. Use of health care resources/costs of care/length of stay 10. Neurodevelopmental status at follow-up:		Lemyre(91) (cont) • Necrotizing enterocolitis (Bell's stage 2) (Bell 1978) • Sepsis • Retinopathy of prematurity (stage 3) (ICROP 2005) • Duration of ETT ventilation (any)	Wilkinson(45) (cont) • Duration of mechanical ventilation via an endotracheal tube (days, or post-menstrual age (PMA) at end); • Duration of any form of respiratory support (mechanical	patent ductus arteriosus [PDA], retinopathy of prematurity [ROP], etc).

<p>Secondary outcomes (cont)</p>	<p>neurodevelopment measured on a validated scale that measures cognitive, motor, behavioural function, or blindness, deafness, or cerebral palsy at about 2 years of age.</p>		<ul style="list-style-type: none"> • Duration of oxygen dependence (days) • Duration of hospital stay (days) • Nasal septal injury • Gastrointestinal perforation 	<p>ventilation, CPAP, high flow nasal cannulae, or oxygen) (days, or PMA at end);</p> <ul style="list-style-type: none"> • Duration of hospitalisation (days, or PMA at end). <p>Complications:</p> <ul style="list-style-type: none"> • Air leak syndromes (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). Note some studies reported this as a continuous outcome and were not able to be included in metaanalysis; • Nosocomial sepsis (defined as positive blood or cerebrospinal fluid (CSF) cultures taken after five days of age). Note some studies used alternative definitions, or did not define sepsis. These were included in meta-analysis; • Gastrointestinal perforation or severe necrotising enterocolitis (NEC) (stage II or more according to Bell's criteria (Bell 1978)). Note: some included studies only reported the <p>Wilkinson(45) (cont)</p> <p>incidence of NEC, and were included in the analysis of this outcome;</p> <ul style="list-style-type: none"> • Weight gain prior to discharge from hospital; • Days to attain full feeds. <p>Neurosensory outcomes:</p> <ul style="list-style-type: none"> • Retinopathy of prematurity (ROP): any stage and stage 3 or greater; 	<p>BPD was defined as respiratory support and/or supplemental oxygen requirement at 36 weeks' corrected GA. If a room-oxygen test was undertaken at 36 weeks' corrected GA before categorizing as BPD, then only infants failing the test were considered to have BPD.17 Grades of IVH were as classified by Papile et al.18 Classification of NEC was as by Bell et al19 and modified by Walsh et al.20</p>
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				<ul style="list-style-type: none">• Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment, developmental delay i.e. IQ 2 standard deviations less than the mean on validated assessment tools such as Bayley's Mental Developmental Index), blindness, hearing impairment requiring amplification.	
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Appendix E: PubMed Search Terms

Search terms used in PubMed search

(((((((((acute[All Fields] AND respiratory[All Fields] AND distress[All Fields]) OR (non[All Fields] AND invasive[All Fields] AND ('positive-pressure respiration'[MeSH Terms] OR ('positive-pressure'[All Fields] AND 'respiration'[All Fields]) OR 'positive-pressure respiration'[All Fields] OR ('positive'[All Fields] AND 'pressure'[All Fields] AND 'ventilation'[All Fields]) OR 'positive pressure ventilation'[All Fields] OR 'intermittent positive-pressure ventilation'[MeSH Terms] OR ('intermittent'[All Fields] AND 'positive-pressure'[All Fields] AND 'ventilation'[All Fields]) OR 'intermittent positive-pressure ventilation'[All Fields] OR ('positive'[All Fields] AND 'pressure'[All Fields] AND 'ventilation'[All Fields]))) OR ('continuous positive airway pressure'[MeSH Terms] OR ('continuous'[All Fields] AND 'positive'[All Fields] AND 'airway'[All Fields] AND 'pressure'[All Fields]) OR 'continuous positive airway pressure'[All Fields] OR ('nasal'[All Fields] AND 'continuous'[All Fields] AND 'positive'[All Fields] AND 'airway'[All Fields] AND 'pressure'[All Fields]) OR 'nasal continuous positive airway pressure'[All Fields])) OR (high[All Fields] AND flow[All Fields] AND ('cannula'[MeSH Terms] OR 'cannula'[All Fields] OR ('nasal'[All Fields] AND 'cannula'[All Fields]) OR 'nasal cannula'[All Fields])) OR ('noninvasive ventilation'[MeSH Terms] OR ('noninvasive'[All Fields] AND 'ventilation'[All Fields]) OR 'noninvasive ventilation'[All Fields] OR ('non'[All Fields] AND 'invasive'[All Fields] AND 'ventilation'[All Fields]) OR 'non invasive ventilation'[All Fields])) OR 'Noninvasive Ventilation'[Mesh]) OR 'Continuous Positive Airway Pressure'[Mesh]) OR 'Acute Chest Syndrome'[Mesh]) AND (((((((('infant'[MeSH Terms] OR 'infant'[All Fields]) OR ('child'[MeSH Terms] OR 'child'[All Fields])) OR 'Child'[Mesh]) OR 'Infant'[Mesh]) OR ('infant, newborn'[MeSH Terms] OR ('infant'[All Fields] AND 'newborn'[All Fields]) OR 'newborn infant'[All Fields] OR 'neonate'[All Fields])) OR 'Infant, Newborn'[Mesh]) OR ('pediatrics'[MeSH Terms] OR 'pediatrics'[All Fields] OR 'pediatric'[All Fields])) OR 'Pediatrics'[Mesh])) AND (((((((('Child, Hospitalized'[Mesh] OR 'Intensive Care Units'[Mesh]) OR 'Intensive Care Units, Neonatal'[Mesh]) OR 'Emergency Medical Services'[Mesh]) OR 'Transportation of Patients'[Mesh]) OR ('intensive care units'[MeSH Terms] OR ('intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields]) OR 'intensive care units'[All Fields])) OR ('intensive care units, neonatal'[MeSH Terms] OR ('intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields] AND 'neonatal'[All Fields]) OR 'neonatal intensive care units'[All Fields] OR ('neonatal'[All Fields] AND 'intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields])))) OR ('intensive care units, neonatal'[MeSH Terms]

OR ('intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields] AND 'neonatal'[All Fields]) OR 'neonatal intensive care units'[All Fields] OR ('neonatal'[All Fields] AND 'intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields])) OR ('transportation of patients'[MeSH Terms] OR ('transportation'[All Fields] AND 'patients'[All Fields]) OR 'transportation of patients'[All Fields] OR ('patient'[All Fields] AND 'transportation'[All Fields]) OR 'patient transportation'[All Fields])) OR ('emergency medical services'[MeSH Terms] OR ('emergency'[All Fields] AND 'medical'[All Fields] AND 'services'[All Fields]) OR 'emergency medical services'[All Fields])) OR (('pediatrics'[MeSH Terms] OR 'pediatrics'[All Fields] OR 'pediatric'[All Fields]) AND ('emergency medical services'[MeSH Terms] OR ('emergency'[All Fields] AND 'medical'[All Fields] AND 'services'[All Fields]) OR 'emergency medical services'[All Fields])) OR ('Intensive Care Units, Pediatric'[Mesh] OR 'Pediatric Emergency Medicine'[Mesh])) AND (('1975/01/01'[PDAT] : '2017/03/15'[PDAT]) AND

English[lang])

Details of search terms used

Domain	MeSH and Text Terms
positive pressure ventilation	'positive-pressure respiration'[MeSH Terms] OR ('positive-pressure'[All Fields] AND 'respiration'[All Fields]) OR 'positive-pressure respiration'[All Fields] OR ('positive'[All Fields] AND 'pressure'[All Fields] AND 'ventilation'[All Fields]) OR 'positive pressure ventilation'[All Fields] OR 'intermittent positive-pressure ventilation'[MeSH Terms] OR ('intermittent'[All Fields] AND 'positive-pressure'[All Fields] AND 'ventilation'[All Fields]) OR 'intermittent positive-pressure ventilation'[All Fields] OR ('positive'[All Fields] AND 'pressure'[All Fields] AND 'ventilation'[All Fields])
nasal continuous positive airway pressure	'continuous positive airway pressure'[MeSH Terms] OR ('continuous'[All Fields] AND 'positive'[All Fields] AND 'airway'[All Fields] AND 'pressure'[All Fields]) OR 'continuous positive airway pressure'[All Fields] OR ('nasal'[All Fields] AND 'continuous'[All Fields] AND 'positive'[All Fields] AND 'airway'[All Fields] AND 'pressure'[All Fields]) OR 'nasal continuous positive airway pressure'[All Fields]
nasal cannula	'cannula'[MeSH Terms] OR 'cannula'[All Fields] OR ('nasal'[All Fields] AND 'cannula'[All Fields]) OR 'nasal cannula'[All Fields]
non invasive ventilation	'noninvasive ventilation'[MeSH Terms] OR ('noninvasive'[All Fields] AND 'ventilation'[All Fields]) OR 'noninvasive ventilation'[All Fields] OR ('non'[All Fields] AND 'invasive'[All Fields] AND 'ventilation'[All Fields]) OR 'non invasive ventilation'[All Fields]
infant	'infant'[MeSH Terms] OR 'infant'[All Fields]
child	'child'[MeSH Terms] OR 'child'[All Fields]
neonate	'infant, newborn'[MeSH Terms] OR ('infant'[All Fields] AND 'newborn'[All Fields]) OR 'newborn infant'[All Fields] OR 'neonate'[All Fields]
pediatric	'pediatrics'[MeSH Terms] OR 'pediatrics'[All Fields] OR 'pediatric'[All Fields]
intensive care units	'intensive care units'[MeSH Terms] OR ('intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields]) OR 'intensive care units'[All Fields]

neonatal intensive care units	'intensive care units, neonatal'[MeSH Terms] OR ('intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields] AND 'neonatal'[All Fields]) OR 'neonatal intensive care units'[All Fields] OR ('neonatal'[All Fields] AND 'intensive'[All Fields] AND 'care'[All Fields] AND 'units'[All Fields])
patient transportation	'transportation of patients'[MeSH Terms] OR ('transportation'[All Fields] AND 'patients'[All Fields]) OR 'transportation of patients'[All Fields] OR ('patient'[All Fields] AND 'transportation'[All Fields]) OR 'patient transportation'[All Fields]
emergency medical services	'emergency medical services'[MeSH Terms] OR ('emergency'[All Fields] AND 'medical'[All Fields] AND 'services'[All Fields]) OR 'emergency medical services'[All Fields]

Appendix F: Forty-Item Data Collection Sheet

1. Study ID
2. Country
3. Dates of study DD/MM/YYYY
4. Duration (months)
5. Type of NIV studied
6. Number of patients transferred on CPAP
7. Age - mean or median SD or IQR (at time of retrieval)
8. If newborn hours of age at Transport
9. Diagnosis 1 / Diagnosis 2 / Diagnosis 3
10. Type of Transport
11. Distances
12. Duration
13. Team composition
14. NIV started by referring facility
15. NIV started by retrieval team
16. Method of NIV generation
17. NIV Interface used
18. Pressure or Flow-rate described before Transport
19. Pressure or Flow-rate described after Transport
20. FiO₂ during Transport
21. FiO₂ after Transport
22. Escalation of ventilation during Transport
23. Intubation during Transport
24. Intubation after Transport
25. BVM during Transport
26. CPR during Transport
27. Apnoea during Transport
28. Desaturation during Transport
29. Bradycardia during Transport
30. Hypotension during Transport
31. Air Leak at any time
32. Other
33. Heart rate
34. Respiratory Rate
35. Work of breathing
36. Oxygen Saturation
37. Fractional inspired oxygen
38. Carbon dioxide measures
39. Blood gas pH
40. Mortality

Appendix G: Twenty-Two-Item Data Collection Sheet

1. Study ID
2. Type of NIV studied
3. Number of patients transferred on NIV
4. Age - mean or median SD or IQR (at time of retrieval)
5. Escalation of ventilation during Transport
6. Intubation during Transport
7. Intubation after Transport
8. BVM during Transport
9. CPR during Transport
10. Apnoea during Transport
11. Desaturation during Transport
12. Bradycardia during Transport
13. Hypotension during Transport
14. Air Leak during Transport or after Transport
15. Heart rate
16. Respiratory Rate
17. Work of breathing
18. Oxygen Saturation
19. Fractional inspired oxygen
20. Carbon dioxide measures
21. Blood gas pH
22. Mortality