The Use and Outcomes of Long-term Non-invasive Ventilation in Infants

by

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ABSTRACT

Background: The use of long-term non-invasive ventilation (NIV), defined as the provision of respiratory support from the upper airway through a mask interface, has increased in infants and older children over the past two decades. A number of studies have been published on NIV use in the overall pediatric population, but there appears to be fewer studies exclusively on the infant population. This finding suggests that the treatment approach to NIV therapy is similar between infants and older children. However, differences in the underlying disorders necessitating NIV, along with differences in sleep and breathing across infancy and childhood suggest that a distinct treatment strategy for these two groups may be appropriate. The aims of this thesis are: (1) to perform a comprehensive review of the literature to establish the data currently available on the use of long-term NIV in infants; and to compare (2) baseline clinical characteristics, (3) technology use, and (4) outcomes of infants and older children on long-term NIV, to determine if infants represent a distinct group with respect to NIV therapy compared to older children.

Methods: Aim (1): A systematic review of the literature on the use of long-term NIV in infants was conducted. Articles were searched for in Ovid Medline, Ovid Embase, CINAHL (via EbscoHOST), PubMed, and Wiley Cochrane Library. The inclusion criteria was studies presenting distinct data on infants (0 to ≤2 years) using long-term NIV (> 3 months of use) outside an acute care setting. Aims (2,3, and 4): A 10-year retrospective chart review of all children using long-term NIV at two pediatric NIV clinics in Alberta, Canada was also performed. Medical charts and sleep laboratory records were reviewed, and demographic, clinical characteristic and health outcome data were extracted. Infants were matched to older children in a 1:2 ratio with respect to sex and the date of NIV start.

Results: Aim (1): A total of 52 studies on infants using long-term NIV were included and analyzed in the systematic review. There were studies on a diverse group of upper airway conditions such as obstructive sleep apnea, laryngo-tracheomalacia, and Pierre Robin sequence. However, studies on neuromuscular and central nervous system disorders looked almost exclusively at spinal muscular atrophy type 1 and central hypoventilation syndrome respectively. While studies on upper airway disorders presented changes in respiratory parameters and discontinuation outcomes, studies on neuromuscular disease reported on hospitalizations and survival outcomes.

Aims (2, 3, and 4): Data for the retrospective review were collected for 622 children, of which 122 (20%) were infants. After matching, 120 infants were paired with 240 older children. There were some similarities between infants and older children, including improvements in respiratory parameters and adherence rates. Differences between the two groups included the underlying condition necessitating NIV, with older children having more upper airway disorders and infants having more cardiopulmonary disease. Infants had more co-morbidities and required more additional technology compared to older children. Reasons for clinic discharge also differed between groups, with infants discharging because of either improvements in the underlying condition or switch to invasive ventilation, while older children were transferred to adult services.

Conclusions: Overall, NIV appears to be a viable method of providing long-term breathing support in infants. Differences in baseline clinical characteristics, sleep and respiratory parameters, technology use, and outcomes such as reasons for clinic discharge were different between infants and older children, supporting the idea that infants represent a distinct population within the overall pediatric NIV population.

PREFACE

The systematic review on the use of long-term non-invasive ventilation (NIV) in infants (Chapter 2) has been submitted as a manuscript for publication. Prabhjot K. Bedi designed the review, read articles for inclusion/exclusion, performed data extraction and analysis, interpreted the data, wrote the initial draft of the manuscript, and completed all revisions until submission. Maria Castro-Codesal designed the review, read articles for inclusion/exclusion, verified the data extraction, and critically reviewed the manuscript. Robin Featherstone developed the search strategy, performed all literature searches, and critically reviewed the manuscript. Mohammed AlBalawi and Bashar Alkaledi read articles for inclusion/exclusion and critically reviewed the manuscript. Anita Kozyrskyj provided guidance on study design and critically reviewed the manuscript. Carlos Flores-Mir provided guidance on study design and review methodology, and critically reviewed the manuscript. Joanna E. MacLean designed the review, read articles for inclusion/exclusion, verified the data extraction, helped with data interpretation, and critically reviewed the manuscript. All authors approved the final manuscript for submission.

The retrospective study comparing the use of NIV for infants and older children (Chapter 3) is being prepared for submission for publication. An abstract for this study has been published as "The Use and Outcomes of Long-term Non-invasive Ventilation in Infants," *American Journal of Respiratory and Critical Care Medicine 2017*, Volume 195;A4105. The abstract was written by Prabhjot K. Bedi and was critically reviewed by Kristie Dehaan, Maria Castro-Codesal, and Joanna E. MacLean.

Research ethics approval was obtained for the retrospective chart review (Chapter 3) from the Health Research Ethics Board at the University of Alberta and University of Calgary, AB, Canada.

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LIST OF ABBREVIATIONS

AHI – apnea-hypopnea index
ALTE – acute life threatening events
BPAP – bi-level positive airway pressure
CCHS – congenital central hypoventilation syndrome
CHS – central hypoventilation syndrome
CNS – central nervous system disorder
CPAP – continuous positive airway pressure
GRADE – Grading of Recommendations Assessment, Development and Evaluation
HVR – hypoxic ventilatory response
IMV - invasive mechanical ventilation
LTM – laryngo-tracheomalacia
NIV – non-invasive ventilation
NMD – neuromuscular disorder
NREM – non-rapid eye movement sleep
OAI – obstructive apnea index
OSA – obstructive sleep apnea
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRS – Pierre Robin Sequence
PSG – polysomnography
REM – rapid eye movement sleep
ROBINS-I – Risk of Bias In Non-Randomized Studies of Interventions
ROHHAD – Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome
SIDS – sudden infant death syndrome
SMA – spinal muscular atrophy
SMA1 – spinal muscular atrophy type 1
SMA2 – spinal muscular atrophy type 1
SMA3 – spinal muscular atrophy type 1

CHAPTER 1: REVIEW OF THE LITERATURE, AIMS, AND HYPOTHESES

Non-invasive ventilation (NIV) has become a standard of care for the treatment of a range of sleep and breathing disorders in infants and older children. These disorders may be caused by underlying conditions such as upper airway obstruction, neuromuscular disease, and central nervous system disease, each with different impacts on sleep and breathing. The development of sleep and breathing physiologically from infancy through childhood can also alter the impact that these disorders have on breathing during sleep and, potentially, the response to treatment. The interaction between underlying conditions, the development of sleep and breathing, and the technology used for NIV may impact the success infants and children have on NIV therapy.

SECTION 1: SLEEP AND BREATHING DISORDERS IN INFANTS AND OLDER CHILDREN

There are a range of sleep and breathing disorders that can present in the pediatric population. Children with certain underlying disease conditions, including upper airway obstruction, neuromuscular disorders (NMD), and central nervous system disease (CNS), are at a higher risk of developing sleep and breathing disorders compared to otherwise healthy children. Some underlying conditions may be more prevalent in infants, while others more common in older children, making it difficult to understand how these children will respond to treatment for their breathing impairment. The relationship between some common pediatric conditions and the development of sleep and breathing disorders will be discussed in the following section.

1.1 Upper airway obstruction

The most common sleep and breathing disorder in any age group is obstructive sleep apnea. There are a number of upper airway conditions presenting in infancy and childhood that can produce compromise of the upper airway and increase the risk of obstructive sleep apnea. These conditions include craniofacial disorders, laryngo-tracheomalacia, adenotonsillar hypertrophy, and obesity (Table 1.1).

Obstructive sleep apnea (OSA) is a breathing disorder that occurs during sleep, and is characterized by intermittent periods of complete or partial obstruction of the upper airway (i.e. apneas and hypopneas respectively).[1,2] The prevalence of OSA is 1-5% in the pediatric population, although there is less data to support this value in the infant population.[3] OSA is typically classified based on the apnea-hypopnea index (AHI) which measures the total number of apneas and hypopneas per hour of sleep. In children, OSA is defined by an AHI $\geq$2 events/hr or an obstructive apnea index (OAI) $\geq$ 1 event/hr.[4] There are currently no standards to define the presence of OSA in infancy. Guidelines on the diagnosis and treatment of OSA in the pediatric population exclude children under 1 year of age[5], making it difficult to determine treatment strategies for this age group. Proper management of OSA is important in order to prevent adverse outcomes such as cardiovascular morbidity, metabolic problems, neurocognitive impairment, and behavioural impairment.[1,6,7]

1.1.1 Craniofacial disorders

Craniofacial disorders, defined as abnormalities of the soft tissue and bones of the face and skull, are one of the most common disorders that present congenitally.[6,8,9] They are organized according to the Whitaker classification into clefts, craniosynostoses, atrophy (hypoplasia), and

neoplasia (hyperplasia), with clefts and synostoses being the most commonly presenting types. Craniofacial disorders result in narrowing of the upper airway, making infants and children with these disorders at a higher risk of developing OSA.[6,9] The prevalence of OSA in craniofacial disorders has been shown to range from 7-67%, depending on the definition of OSA used and the underlying conditions examined.[10] There are a number of craniofacial syndromes that can present in the pediatric population (Table 1.1), with the most commonly studied syndromes being cleft lip and/or palate, Pierre Robin sequence, and craniosynostosis.

Cleft lip and/or palate, one of the most common congenital malformations (1 in 700 live births), occurs due to failure of the fusion of the medial and lateral nasal processes with the maxillary processes.[8] It can occur unilaterally or bilaterally, and can affect both the soft and hard palate. Although the majority of clefts occur in isolation, there are over 200 syndromes that can also present with cleft lip and/or palate, including Pierre Robin sequence and Treacher Collins syndrome (Table 1.1).[8,9,11] Infants and children with cleft lip and/or palate are at a higher risk of developing OSA because the presence of a cleft results in a small midface and posteriorly placed jaw, leading to narrowing of the airway passages. A prospective study on 50 infants with cleft lip and/or palate either in isolation, as part of a syndrome, or with Pierre Robin sequence showed that 69%, 100%, and 86% of these infants respectively had an obstructive-mixed AHI > 3 events/hr, which was the cut-off for clinically significant OSA.[12]

Pierre Robin Sequence consists of a triad of findings including a small sized jaw (micrognathia), enlarged tongue (glossoptosis), and resultant airway obstruction.[13] It is the most common cause of syndromic micrognathia[8], and can also present with cleft lip and/or palate.[6,8] The craniofacial

abnormalities seen in Pierre Robin sequence, and subsequent airway obstruction, can increase the risk of OSA in these infants.[13-15] A retrospective study on 13 infants with Pierre Robin sequence showed that 11/13 (92%) had OSA, with a mean obstructive AHI of 33.5 events/hr (range 0 to 85.7 events/hr).[16]

Craniosynostosis is characterized by the premature fusion of one or more sutures of the skull, and is present in about 1 in 2500 births.[6] About 40% cases of craniosynostosis occur in conjunction with another syndrome, and the majority of cases occur because of a mutation in the fibroblast growth factor receptor gene.[17] The premature fusion of the skull results in restricted growth of the midface region, resulting in midface hypoplasia. A prospective study of 97 infants and children with craniosynostosis showed that the prevalence of OSA ranged from 60-75%. The same study also showed that infants and children less than three years of age had the highest risk of OSA.[18]

The airway compromise seen in infants and children with craniofacial disorders predispose them to a higher risk for OSA. The majority of craniofacial disorders are congenital and are therefore more likely to present with OSA in infancy. These impairments, and the risk of OSA, can decrease with age due to growth of the facial bones and airway passages, relieving some of the airway obstruction.

1.1.2 Laryngo-tracheomalacia

Laryngo-tracheomalacia is the most common cause of stridor or noisy breathing in the infant population. It occurs due to a laxity of the pharyngeal or tracheal cartilage, which results in

involution of the soft tissue, and airway obstruction.[19,20] This pathophysiology increases the risk of OSA in infants and children with this disorder. Laryngo-tracheomalacia most often occurs congenitally, and presents with breathing impairment during both wake and sleep. In contrast, the late onset of this disorder, which occurs in children > 2 years of age, presents with breathing impairment predominantly during wake, and minimally during sleep. Therefore, infants with congenital laryngo-tracheomalacia are more vulnerable to OSA than older children because breathing impairment occurs for a longer period of time. A review of studies examining OSA in infants and children with laryngomalacia showed that the AHI in the congenital group was higher than that in the late onset laryngomalacia group (20.4 events/hr vs 14.0 events/hr).[21] The majority of cases of congenital laryngo-tracheomalacia will resolve by two years of age due to maturation and growth of the pharyngeal muscles and tracheal cartilage, once again making OSA secondary to laryngo-tracheomalacia a disorder primarily of infancy.[20,22,23]

1.1.3 Adenotonsillar hypertrophy

Adenotonsillar hypertrophy, the overgrowth of adenoid and tonsillar tissue in the back of the upper airway, is the most common cause of OSA in older children.[4,24,25] Overgrowth of the adenoid and tonsillar tissue leads to narrowing of the upper airway and difficulty breathing, increasing the risk of OSA.[4] The size of the adenoids and tonsils in children with OSA have been shown to be significantly larger than otherwise healthy matched controls. A study of 37 children diagnosed with adenotonsillar hypertrophy showed that 20 (54%) had OSA, with a total mean AHI of 13.4 ± 9.2.[26] The typical growth period for adenoids and tonsils is 2-8 years, and therefore, OSA as a consequence of adenotonsillar hypertrophy is more likely to affect older children than infants.[7]

1.1.4 Obesity

The link between obesity and breathing impairment has been well established, and shows that obese children are at a higher risk of developing OSA.[1,27,28] Children who are obese have fatty infiltrates within the compartments of their upper airway structure and neck, which contributes to narrowing and collapsibility of the upper airway, and an increased risk of OSA. A study of 151 overweight children showed mild OSA in 27.1% of the population and moderate/severe OSA in 61.5% of the population on a polysomnograpy.[29] OSA is more common in older children than infants, and with the prevalence of childhood obesity increasing[30], the number of older children presenting with OSA secondary to obesity is also likely to increase.

1.1.5 Summary of sleep and breathing disorders in upper airway obstruction

Infants more commonly present with OSA secondary to congenital or developmental abnormalities of the upper airway, including craniofacial disorders and laryngo-tracheomalacia. On the other hand, older children present with upper airway obstruction and subsequent OSA as a result of adenotonsillar hypertrophy or obesity. The risk of OSA secondary to upper airway obstruction appears to be higher in infancy, and decreases with age due to the growth of bony structures that may open up the airway. The predisposition of smaller airways to collapse, along with differing underlying conditions resulting in OSA, may affect how infants respond to breathing support used to treat upper airway obstruction, compared to older children.

1.2 Neuromuscular disorders

NMD impact respiratory muscles, and the weakness of these muscles result in impaired ventilation. Common types of sleep and breathing disorders seen in NMD include OSA, and hypoventilation. The presence of OSA and hypoventilation are related to the underlying disease condition and the age of the child. Commonly studied NMD that are known to increase the risk of OSA and hypoventilation in infants and older children include spinal muscular atrophy, myotonic dystrophy, Duchenne muscular dystrophy, and kyphosis and scoliosis (Table 1.1).

Hypoventilation is characterized by insufficient ventilation to maintain a normal carbon dioxide level, resulting in an increase in the carbon dioxide level in the blood. Hypoventilation can be the result of a decrease in tidal volume because of low respiratory muscle strength or a decrease in the number of breaths because of impairment in breathing control. Central sleep apnea, while more common in central nervous system disorders, is also seen in the context of NMD. It is characterized by exclusive, or a predominance of, complete or partial pauses in breathing without evidence of respiratory effort (i.e. central apneas and hypopneas) during sleep. Depending on the severity of central sleep apnea, it may or may not result in hypoventilation.

1.2.1 Spinal muscular atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects motor neurons in the spinal cord and brainstem. It is the most common genetic neuromuscular disorder causing death in the infancy period.[31,32] SMA results in a generalized, progressive weakness of all muscles, leading to respiratory impairment and sleep and OSA and hypoventilation. SMA is classically divided into three types according to the time of onset and disease severity. Type 1 SMA (SMA1) is the most severe type with infants incapable of sitting, and usually results in

death before the age of two. Type 2 SMA (SMA2) is a milder form of muscular atrophy in both infants and older children where children are able to sit but not walk. Type 3 SMA (SMA3) is the mildest form where children are able to stand and walk but may lose these function in later life.[31-34] OSA and hypoventilation are seen in all types of SMA. A study on 9 infants with SMA1 and SMA2 ages 2-33 months showed a mean AHI of 2.1 events/hr (range 0.5 - 55.8 events/hr), oxygen desaturations, and high levels of transcutaneous carbon dioxide.[35] Another study on 12 older children with SMA1 and SMA1 ages 7.8 ± 1.9 years showed that 7 (58%) children had respiratory events and oxygen desaturations secondary to hypoventilation.[36] Sleep and breathing disturbances secondary to OSA and hypoventilation occur in both infants and older children with SMA. SMA1 has a more rapidly deteriorating course compared to children with SMA2 and SMA3 and, therefore, require early respiratory support and may eventually succumb to respiratory failure.

1.2.2 Myotonic dystrophy

Myotonic dystrophy is the most common inherited muscle disorder in children, and can occur congenitally or have a late onset.[37] In addition to causing muscle weakness, it also affects multiple organs including the brain and heart, and can present with some craniofacial anomalies. Myotonic dystrophy can cause diaphragmatic weakness, upper airway obstruction, and impairments in central ventilatory drive, increasing the risk of hypoventilation, OSA, and central sleep apnea. It is also associated with increased periodic limb movements during sleep.[38] A study of 21 older children with myotonic dystrophy showed disturbances in sleep on PSG caused by apneas, periodic limb movements or both in 29%, 38%, and 5% of children respectively.[39] There is little data on the link between congenital myotonic dystrophy and sleep and breathing

disorders in infants; however, a case study of one infant showed the presence mixed central and obstructive apneas resulting in respiratory distress.[40] With little data from infants with myotonic dystrophy, it is unclear whether sleep and breathing impairments are similar in infants compared to older children and how treatment may differ.

1.2.3 Duchenne muscular dystrophy

The majority of data on sleep and breathing disorders in children with NMD comes from studies on Duchenne muscular dystrophy. This disorder is an x-linked dystrophy due a defect in the dystrophin gene, which leads to progressive muscle deterioration. The generalized muscle weakness that occurs in this dystrophy increases the risk of OSA and hypoventilation as the diseases progresses through childhood. A study on 44 children with Duchenne muscular dystrophy showed that these children had a higher number of obstructive respiratory events, including apneas and hypopneas, compared to otherwise healthy children.[41] Another study on 32 children with Duchenne muscular dystrophy found that 31% had OSA and 32% had hypoventilation. It also showed that OSA was more prevalent in the first decade of life, whereas hypoventilation was more common at the beginning of the second decade.[42] Duchenne muscular dystrophy is a disorder that progresses with age, and therefore the OSA and hypoventilation seen this group occurs almost exclusively in older children.

1.2.4 Kyphosis and scoliosis

Kyphosis and scoliosis are characterized by an abnormal curvature of the spine in the sagittal and coronal plane respectively. They can be congenital or acquired and can occur together. Scoliosis is the most common musculoskeletal complication of NMD seen in children.[37] It can lead to

decreased chest wall and lung compliance, ultimately increasing the work of breathing and leading to hypoventilation. There are limited studies in infants and children on the relationship between kyphosis and scoliosis and hypoventilation. A review of the available studies, however, shows that scoliosis is a reported predictor for nocturnal hypoventilation.[43]

1.2.5 Summary of sleep and breathing disorders in neuromuscular disease

NMD are a diverse group of conditions that can produce muscular weakness, including the muscles involved in respiration. The most common sleep and breathing disorder that occurs in the NMD population is hypoventilation, but underlying disease characteristics such as craniofacial anomalies or involvement of the CNS can also increase the risk for OSA and central sleep apnea. The most commonly studied NMD in infants and in older children is SMA1 and Duchenne muscular dystrophy respectively. Differences in the type of sleep and breathing disorders seen in different conditions, in addition to differences in the progression of muscular weakness seen with NMD, means that a different approach to respiratory support may be needed for infants and older children with NMD.

1.3 Central nervous system disease

CNS disorders can cause impairments in the central control of breathing, resulting in central sleep apnea and hypoventilation. A number of CNS disorders presenting in infancy and childhood can cause central hypoventilation (Table 1.1). The relationship between CNS disorders, central sleep apnea, and hypoventilation has not been well characterized, but there is some data in the context of congenital central hypoventilation syndrome (CCHS), rapid onset

obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) syndrome, and myelomeningocele with Arnold-Chiari type 2 malformation.

1.3.1 Congenital central hypoventilation syndrome

CCHS is a rare disorder in which there is impaired central control of breathing due to an abnormality in the PHOX2B gene, which is involved in the development of the autonomic nervous system.[44,45] CCHS is associated with hypoventilation, and while the mechanism behind this hypoventilation is not well understood, it is hypothesized that a deficit in the central integration of chemoreceptor inputs may be responsible for autonomic dysfunction and decreased central respiratory drive.[46] CCHS presents with periods of central apnea and hypoventilation, which worsen during sleep. A study of 9 infants with CCHS during sleep showed significantly worsened hypoventilation throughout their sleep.[47] Most cases of CCHS were thought to present at birth, with diagnosis within the first six months of life; however, it is now clear that CCHS has a broad spectrum of disease, with the more severe cases presenting in early life and milder forms potentially not detected until adulthood.

1.3.2 Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome

ROHHAD syndrome has similar respiratory impairment compared to CCHS, but differs in that the age of presentation is later (typically after 1.5 years of age) and it is associated with rapid onset obesity and hypothalamic dysfunction. [46,48] It has only recently been distinguished as a separate disorder from CCHS.[46] The first clinical symptom typically seen in ROHHAD

syndrome is rapid weight gain, which can be an excess of 15kg per year. It is also associated with the development of hypoventilation due to autonomic nervous system dysregulation, although the PHOX2B gene mutation is characteristically not present in this group.[46] A study of 23 children with ROHHAD syndrome showed an onset of alveolar hypoventilation in all children at a median age of 6.2 years.

1.3.3 Myelomeningocele and Arnold-Chiari malformation type 2

Myelomeningocele is a congenital birth defect in which the spine and spinal canal do not close before birth.[37,49] It can be associated with Arnold-Chiari malformation type 2, where a part of the cerebellum, brainstem, and fourth ventricle in the brain herniate through an opening in the skull and into the spinal canal.[50] Infants and children with myelomeningocele and Arnold-Chiari malformation type 2 are at a higher risk for both central sleep apnea and OSA secondary to spinal lesions, brainstem abnormalities, and disorders of upper airway control.[37,46] A study of 83 children with myelomeningocele and Arnold-Chiari malformation type 2 showed that breathing was moderately/severely impaired in 17 (20%) of children, who had a median AHI of 16.6 events/hr (range 8.1-105 events/hr). In addition, 12 (71%) children had central apneas, 5 (29%) had primarily obstructive apneas, and two-thirds of these patients also presented with hypoventilation.[51]

1.3.4 Summary of sleep and breathing disorders in central nervous system disease

CNS disorders presenting in infancy and childhood can increase the risk of central hypoventilation and central sleep apnea. These disorders may present in different age groups, such as CCHS which occurs congenitally in infants, and ROHHAD syndrome which presents in

older children. Despite a similar pathophysiology, CCHS causes predominantly central sleep apneas and hypoventilation in infants, while ROHHAD can cause OSA in addition to central sleep apnea and hypoventilation in older children. Given the differences in disorders presenting by age, strategies to support breathing during sleep may differ in infants and children with CNS disorders.

1.4 Summary of sleep and breathing disorders in infants and older children

There are a number of upper airway, NMD, and CNS disorders in the pediatric population that can increase the risk of sleep and breathing disorders like OSA, central sleep apnea, and hypoventilation. While some conditions may begin in infancy and continue on into childhood and adolescence, there are a number of conditions that occur predominantly in either the infant or child population. These include congenital syndromes, laryngo-tracheomalacia, and SMA1 in the infant population, and adenotonsillar hypertrophy, obesity, and Duchenne muscular dystrophy in the older child population. It is unclear whether the differences in disorders by age necessitate a difference in treatment approach to the use of long-term NIV.

SECTION 2: THE PHYSIOLOGY OF SLEEP AND BREATHING THROUGH INFANCY AND CHILDHOOD

Sleep and breathing are consistently evolving from birth through childhood. These changes in normal physiology add to the challenge of identifying how sleep and breathing disorders, such as OSA, central sleep apnea, and hypoventilation, may affect treatment response in those who get treatment. This means that understanding whether infants and children have differences in how they respond to treatment requires an understanding of the normal physiological progress of sleep and breathing with age. The following section will describe the physiological changes in sleep and breathing across infancy and childhood.

1.5 The physiology of sleep through infancy and childhood

Sleep is a dynamic, physiological process that is critical for developmental progress. Sleep starts before birth but is not fully developed, with changes in the predominant sleep stages, duration and timing of sleep, as well as arousal responses over the first years of life. The maturation of sleep is a marker of brain development and, hence, sleep disruption is associated with the disruption of physical and neurocognitive development.

1.5.1 Sleep stages and sleep stage distribution

To understand the physiology of sleep and breathing, knowledge of commonly used sleep terminology is important. Infant sleep is classified into two distinguishable patterns, active sleep and quiet sleep. Active sleep in newborn infants is characterized by sucking motions, twitching, facial expressions, limb movement, and irregular breathing. Quiet sleep is characterized by muscle paralysis.[52] A third stage, called indeterminate sleep, is used when features of both active sleep and quiet sleep are present.[53] The onset of sleep in infants initially occurs through active

sleep, but then transitions to during non-rapid eye movement (NREM) sleep by about 6 months of age. All the features of adult sleep should be identifiable between 2 and 6 months of age with the term rapid eye movement (REM) sleep used to describe deeper sleep with characteristics of muscle paralysis, and NREM sleep applied to light sleep (including stage N1 and N2) as well as slow wave sleep (stage N3).[54] This means that the terms used to describe sleep change between infancy and childhood.

The proportion of time spent in each sleep stage also differs with age. A term-born infant will spend approximately equal time in active sleep and quiet sleep, whereas by 6 months of age, the proportion of REM sleep decreases to about 25% of the total sleep time, as seen in adults. The greater amount of time young infants spend in REM sleep predisposes them to developing breathing impairments, as respiratory events such as OSA are more predominant during REM sleep. This characteristic of REM sleep occurs because of a reduction of muscle tone in skeletal muscles during REM sleep, causing narrowing of the airway.[55] Changes in sleep stage distribution over the first year of life contribute to improvements in breathing disorders.

1.5.2 Timing of sleep

Timing of sleep and circadian rhythm also differ across infancy and childhood. Infants are born without an established circadian rhythm of sleep, which means that their sleep does not yet follow the 24h sleep-wake pattern seen in older children and adults.[52,56] Development of circadian patterns of sleep begin after one month of age, and are influenced by light exposure and feeding patterns.[57,58] The circadian rhythm for wake develops before the circadian rhythm for sleep, at about 45 days and 2 months respectively.[58-60] Also around 2 months of age, sleep

becomes more consolidated during the night, similar to the pattern seen in older children and adults. Diurnal patterns of sleep, with longer periods of sleep during the night and shorter periods during the day, are established by 3 months of age. By 6 months, infants have a circadian rhythm that is physiologically similar to that of adults with sleep occurring predominantly at night and shorter amounts of sleep during the day.[52,59,61,62] The immature circadian rhythm patterns seen in infants may impact the treatment strategies required for sleep and breathing disorders in this age group, as they are constantly waking up and sleeping throughout the day, as opposed to a single sleep period during the night seen in older children.

1.5.3 Sleep duration

Infants spend more time in sleep than older children and, therefore, may have greater effects from the problems arising with breathing during sleep. The total amount of time spent in sleep is inversely related to age, with the greatest decrease over the first six months of life.[62] While a newborn infant spends 16-18 h/day in sleep[59,63], sleep duration decreases to 13.6 h/day by age three months; 12.9h/day by age six months; 12.6h/day from one to two years of age; 11.9h/day from ages two to five years; and 9.2h/day for ages six to twelve years.[62] Afterwards, the total sleep duration remains relatively unchanged through childhood and adolescence.[64] The American Academy of Sleep Medicine recently published consensus for sleep duration in children for optimal health highlights the decrease in sleep duration requirements with increasing with age (Table 1.2).[65] It is unclear, however, whether higher amounts of sleep in infants may also impact treatment strategies with respect to breathing support from therapies such NIV.

1.5.4 Arousals

The physiology of arousals, defined as transient changes in sleep state or stage, also differ between infants and older children. Arousal act as a protective mechanism against respiratory events that occur during sleep by lightening sleep or causing an awakening, resulting in termination of the respiratory event.[7,59] Arousal thresholds are inversely related to age, with infants having the highest threshold. Infants have a higher number of arousals compared to older children, meaning they are more likely to arouse from sleep to terminate a respiratory event when compared to older children[7,59]

1.5.5 Summary of the physiology of sleep through infancy and childhood

There are distinct differences in normal sleep physiology across infancy and childhood. This includes a higher proportion of REM sleep, greater sleep duration, a developing circadian rhythm, and a higher arousal threshold in infants compared to older children. The greatest change in sleep physiology occurs across the first 6 months of life, making it difficult to determine how infants may respond to treatment therapy compared to older children.

1.6 The physiology of breathing through infancy and childhood

Similar to the changes in sleep, the physiology of breathing also changes across infancy and childhood. Breathing begins before birth and continues to mature in early life, making the control and stability of breathing lower in early life. This makes infants susceptible to impairments and breathing and it is unclear how they may respond to respiratory support compared to older children.

1.6.1 Control of breathing

Central and peripheral control of breathing is immature and variable at birth, and matures with increasing age. An example of this is the change in the hypoxic ventilatory response (HVR), defined as the response of ventilation to exposure to low oxygen. Older children have a HVR similar to adults, and experience a period of prolonged hyperventilation in response to hypoxia, which declines after about half an hour to values above baseline.[66] Term-born infants, on the other hand, have a distinct, biphasic HVR, with an initial period of sustained hyperventilation, followed by a decrease in ventilation at or below baseline values.[67-70] The biphasic response seen in infants may last anywhere from a few weeks up to the first 6 months of life, after which the response becoming similar to that in adults.[70]

1.6.2 Changes in breathing patterns

Respiratory rate, defined as the number of breaths per minute, decreases from infancy to early adolescence.[59,71] Respiratory rate changes from about 44 beats per minute at birth to 26 breaths per minute by two years of age[72], and reaches adult values of 18 breaths per minute by early adolescence.[71] The greatest decline in respiratory frequency occurs within the first two years of life.[72] Respiratory rate also varies with sleep state and sex, with higher rates and variability seen during REM sleep and in boys respectively.[71,73,74]

Patterns of breathing, such as periodic breathing, also change with increased age and maturation of breathing control. Periodic breathing is a normal respiratory pattern seen in pre-term and newborn infants, characterized by regular cycles of central apnea followed by rapid, shallow breathing.[75-77] Periodic breathing is highest at birth and continues decreasing through the first two years of life.[76,77] The higher prevalence of periodic breathing in pre-term infants compared

to term-born infants suggests a relationship with the immaturity of the ventilatory control system. This pattern of breathing, which is considered normal in most infants, is more common during sleep than wake.[71] Normal infants 12-18 months of age may have periodic breathing for 1-2.5% of their total sleep time[78,79], after which the presence of periodic breathing is considered abnormal.[77] Periodic breathing has been associated with prolonged apneas[80] and a risk of sudden infant death syndrome. The presence of periodic breathing may change the approach to treatment including the use of long-term NIV.

1.6.3 Oxygen desaturations

There is a higher variability in oxygen saturations in infants compared to older children. While baseline oxygen saturations do not change with age, infants normally have more oxygen desaturations compared to older children. In fact, the majority of infants have acute decreases in oxygen saturations, and these transient decreases improve with age and the reduction of periodic breathing.[81] With increasing age, control of breathing stabilizes and it is uncommon to see oxygen desaturations in older children without the presence of sleep and breathing disorders.[59,71]

1.6.4 Respiratory events during sleep

Respiratory events, including obstructive, mixed, and/or central apneas and hypopneas, occur at low frequency after birth. In the early months of life, central respiratory events are common with decrease in the frequency to 3 events/h by 9 months of age. Obstructive respiratory events up to 3 events/h are common in infants under 6 months of age and decrease to 1 event/h by 9 months of age.[59] An AHI of greater than 1 event/h of sleep are considered abnormal in infants more than one year of age. There are no current guidelines to define normal cut-off AHI values for infants

less than one years of age. Greater instability in both sleep and breathing parameters make it more challenging to distinguish normal and abnormal breathing patterns in infants; with less variability, this distinction is easier in older children.[59,71]

1.6.5 Summary of the physiology of breathing through infancy and childhood

There were differences in breathing across infancy and childhood, including increased respiratory rates in infants, more periodic breathing, more oxygen desaturations, and increased respiratory events. Respiratory events including periodic breathing, oxygen desaturations apnea, and hypopnea are part of the normal pattern of breathing development in infants making it challenging to determine which infants may require treatment to support breathing during sleep.

1.7 Summary of the physiology of sleep and breathing through infancy and childhood

Both sleep and breathing are processes that continue to mature and develop with age. Characteristics of sleep in infants, such as increased sleep duration and a higher proportion of REM sleep, predispose them to more respiratory events that occur during sleep such as apneas and hypopneas, compared to older children. In addition, the immaturity of breathing patterns and control of ventilation in infants also makes them more susceptible to respiratory events occurring secondary to sleep and breathing disorders, such as OSA. The distinct characteristics of sleep and breathing in infants make it difficult to determine how they might respond to breathing support, such as NIV, for the treatment of these disorders.

SECTION 3: NON-INVASIVE VENTILATION TECHNOLOGY

Non-invasive ventilation (NIV) is a method of providing breathing support through an interface outside the airway. Over the past two decades, there has been a shift from hospital-based to home-based ventilation strategies. This shift has resulted in NIV emerging as a standard of care for treating many sleep and breathing disorders in infants and older children. NIV technology and the changes in its use over time in infants and older children is described below.

1.8 Definition of long-term non-invasive ventilation

NIV is used to provide breathing support from outside the airway through an interface.[82-84] The interface is commonly a nasal or full face mask, which is attached to a ventilator via tubing.[85] NIV is an alternative to invasive mechanical ventilation where the interface is inside the body, either through the nose, mouth, or inserted directed into the throat through a hole in the neck.[86,87] Long-term NIV is defined as continuous NIV use for greater than 3 months.

1.8.1 Common types of non-invasive ventilation

The two most commonly used modes of NIV are continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP).[82,84] CPAP is a process where a fixed, continuous pressure of air flows into the airway, helping to keep the airway patent. It has been shown to increase lung volume[88], decrease the work of breathing[22,89,90], and may facilitate gas exchange.[91] BPAP is a method where dual pressures are delivered by the ventilator, and there is a higher inspiratory pressure and a lower expiratory pressure.[85,92] The lower pressure phase allows for easier expiration for infants and children who require higher levels of inspiratory pressure. The provision of dual, alternating pressures by the BPAP machine means a back-up rate can be set

up. Since the machine is triggered by breathing, if the back-up rate for ventilation is not being met, the machine will deliver a breath to the patient. BPAP also decreases the work of breathing, and improves tidal volume and minute ventilation, thereby facilitating gas exchange.[90,93]

The decision to use CPAP or BPAP depends on a number of factors, including primary underlying disease conditions, NIV pressures, and the age group being ventilated. Since CPAP pneumatically stents the airway, it is ideal in conditions where there is an obstruction of the upper airway, as it helps keep the airway patent.[85] BPAP is effective in disorders causing neuromuscular and skeletal weakness, as it helps to unload respiratory muscles and decrease ventilatory effort.[22] It is also effective in disorders that result in impairment of central ventilatory control, as the ventilator can deliver a breath if a back-up ventilation rate is not maintained.

1.9 Factors contributing to the increased use of non-invasive ventilation over time

Over the past two decades, there has been a shift from hospital-based ventilation towards long-term home ventilation. This shift has allowed for an increasing number of infants and older children to use long-term NIV at home. There are a number of drivers that have allowed for this change to take place.

1.9.1 Advancements in medicine and critical care

Improvements in medicine have led to an increasing number of medically complex infants and older children surviving formerly fatal conditions.[94-96] The survival rate of infants born prematurely with chronic lung disease, or with congenital anomalies has increased over the past two decades.[97,98] The longevity of survival has also increased for older children with chronic pulmonary conditions such as cystic fibrosis[99,100] and neuromuscular disorders like Duchenne

muscular dystrophy.[101,102] Improvements in survival, along with the development of chronic respiratory sequelae that requires ventilatory support, have caused NIV use to increase in infants and older children.[94,103,104]

1.9.2 Improvements in NIV technology

Improvements in NIV ventilator technology, including mask interfaces, have also led to the increased expansion of infants and children using NIV.[103,105,106] The production of light-weight, portable, and easy-to-use ventilators have allowed NIV to be delivered from a home-based setting.[85,103] The development of well-fitting nasal and full-face masks for older children, including customized nasal masks, have increased the use of NIV technology by reducing mask complications such as air leak and skin breakdown.[107-111] The development of NIV masks for older children has increased; however, despite an increasing number of infants using NIV therapy, there appears to be minimal research into the development of nasal masks in infants.[111]

1.9.3 Avoiding the complications of invasive mechanical ventilation

The use of long-term NIV has also increased because of the ability to avoid complications associated with invasive ventilation.[86,87,112] These include surgical complications such as inflammation and infection at the site of tracheostomy insertion. There are also long-term complications of invasive mechanical ventilation, such as longer hospital stay, upper airway infections, swallowing dysfunction, and delayed speech and language development.[5,6] These morbidities have resulted in clinicians, parents, and caregivers opting for less invasive modes of long-term respiratory support, driving up the rates of NIV use in both infants and older children.

1.9.4 Recognition by clinicians and families of NIV as a feasible option for providing long-term respiratory support

The use of home NIV has gained popularity because of the increasing recognition of the importance of home-based care for infants and children.[113] For clinicians, one of the goals of long-term ventilation is to provide safe, effective respiratory support in a comfortable environment. The pressure to decrease the length of hospitalizations, in addition to the increased understanding that an acute care setting is both a socially and developmentally inappropriate environment for children, has contributed to the rise in domiciliary NIV.[106,114,115]

1.9.5 Summary of factors contributing to the increased use of non-invasive ventilation over time

There has been a shift from invasive to non-invasive modes of long-term ventilation, and this shift has primarily been driven by advancements in medicine and technology, avoidance of complications associated with invasive mechanical ventilation, and an increased recognition by clinicians and caregivers of NIV as a viable method of providing long-term ventilatory support.

1.10 Summary of non-invasive ventilation technology

NIV is a method of providing breathing support from an interface outside the airway. The use of NIV in both infants and older children has increased due to advancements in medicine and technology, the need to avoid complications associated with invasive mechanical ventilation, and increased recognition of clinicians and caregivers of NIV as a viable respiratory therapy. It has emerged as the standard of care for treating infants and older children with SDB. While our understanding of NIV in older children with SDB has increased, there is less evidence for its use

and outcomes in infants. Fundamental differences in sleep and breathing pathophysiology suggest that infants and older children may respond differently to NIV treatment.

SECTION 4: AIMS AND HYPOTHESES

The increase in the use of long-term NIV to treat sleep and breathing disorders in infants and children has likely been driven by advancements in medicine and NIV technology, and an increased recognition by clinicians and caregivers of NIV as a feasible option for providing long-term respiratory support. Despite the fact that more infants and children are being ventilated with NIV, there appears to be less data around the use of this therapy in infants. Without evidence to say otherwise, it appears that the approach to NIV therapy is likely similar between infants and older children. However, it is clear that underlying disease conditions, as well as the physiology of sleep and breathing, differ between infants and older children. These differences suggest that infants may face separate challenges when using NIV therapy, and may require a different approach to treatment.

The overall aim of this study is to compare the use of long-term NIV in infants and older children to determine whether infants represent a distinct group within the overall pediatric NIV population. The specific aims of this study are:

Aim 1: To perform a comprehensive review of the evidence currently available around the use of long-term NIV in the infant population.

Aim 2: To compare the population characteristics of infants and older children using long-term NIV. Population characteristics will include age, sex, ethnicity, primary underlying condition, co-morbidities, and baseline respiratory parameters.

Aim 3: To compare the treatment strategies for infants and older children using long-term NIV. These include history of prior airway surgery, NIV type, mask type, and use of any additional technology (ex. supplemental oxygen).

Aim 4: To compare the outcomes for infants and children using long-term NIV. Outcomes will include changes in respiratory parameters from a diagnostic to titration PSG, physician reported improvements, adherence rates, and reasons for clinic discharge.

Hypothesis: Underlying disease categories will differ between infants and older children because infants have more congenital conditions, such as craniofacial malformations, SMA1, and CCHS. Baseline sleep and respiratory parameters will also differ between infants and older children because of changes in sleep and breathing physiology with age. Older children will likely have a greater history of prior airway surgery, such as removal of the adenoids and tonsils, as the growth of this tissue occurs in older children. Given the manual dexterity of infants, it is likely that adherence rates will be higher in infants compared to older children because they cannot remove the NIV masks. Outcomes such as reasons for clinic discharge will also differ between infants and older children.

Table 1.1: Disease conditions in infants and older children that may be associated with sleep and breathing disorders.

Underlying disorder	Disease conditions predominantly in infants	Disease conditions predominantly in older children
Upper airway	❖ Craniofacial disorders ▪ Clefts ➢ Isolated cleft lip and/or palate ➢ Syndromic cleft lip and/or palate (Pierre Robin sequence, Treacher Collins syndrome, Stickler syndrome, Goldenhar syndrome, Nager syndrome) ▪ Craniosynostoses ➢ Isolated ➢ Syndromic (Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, Muenke syndrome, Saethre-Chotzen, Carpenter syndrome) ❖ Laryngeal/tracheal disorders ▪ Laryngo-tracheomalacia ▪ Vocal cord palsy ▪ Subglottic stenosis ▪ Laryngeal webs/cysts	❖ Adenotonsillar hypertrophy ❖ Obesity ❖ Syndromic (Prader-Willi syndrome, Down synrome) ❖ Achondroplasia
Neuromuscular/Skeletal	❖ Motor neuron disease (spinal muscular atrophy 1, 2) ❖ Congenital myotonic dystrophy ❖ Congenital myopathies (Nemaline, central core, centronuclear, multicore, minicore) ❖ Mitochondrial myopathies ❖ Neuromuscular junction (congenital myasthenia) ❖ Spinal cord injury ❖ Skeletal - kyphoscoliosis, Achondroplasia	❖ Motor neuron disease (spinal muscular atrophy 2, 3) ❖ Dystrophinpathies (Duchenne muscular dystrophy, Becker muscular dystrophy) ❖ Non-dystrophinpathies (Limb girdle muscular dystrophy, Fascioscapulohumer, Emery Dreifuss) ❖ Myotonic dystrophy ❖ Peripheral nerve (Hereditary motor and sensory neuropathies, hereditary sensory autonomic neuropathy, phrenic nerve injury, polyneuropathy, Guillain Barre syndrome) ❖ Neuromuscular junction (Myasthenia gravis) ❖ Spinal cord injury

		❖ Skeletal - kyphoscoliosis, Achondroplasia
Central nervous system	❖ Congenital central hypoventilation syndrome ❖ Myelomeningocele/Arnold Chiari 2 malformation ❖ Apnea of prematurity ❖ Cerebral palsy ❖ Achondroplasia ❖ Mitochondrial disorders (Leigh syndrome, Kearns-Sayre syndrome, inherited mitochondrial myopathies)	❖ Central hypoventilation syndrome ❖ Obesity hypoventilation syndrome ❖ Rapid-onset obesity hypothalmic dysfunction and autonomic dysregulation (ROHHAD) syndrome ❖ Prader-Willi syndrome ❖ Acquired brain injury (infarctions, ischemia, encephalitis, tumors) ❖ Achondroplasia ❖ Familial dysautonomia

Table 1.2: American Academy of Sleep Medicine consensus for recommended duration of sleep in the pediatric population.[116]

Age	Recommended sleep duration (h/day)
0-4 months	Not available*
4-12 months	12-16
1-2 years	11-14
3-5 years	10-13
6-12 years	9-12
13-18 years	8-10

*sleep recommendations for infants less than 4 months of age are not provided because of a normal wide variation in duration and patterns of sleep and insufficient evidence of association with health outcomes.

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CHAPTER 2: LONG-TERM NON-INVASIVE VENTILATION IN INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 ABSTRACT

Context: The use of long-term non-invasive ventilation (NIV) for treating sleep and breathing disorders in the pediatric population has increased over the past decade; however, there is less data on NIV outcomes in infants.

Objective: To systematically review the use and outcomes of long-term NIV in infants.

Data Sources: Ovid Medline, Ovid Embase, CINAHL (via EbscoHOST), PubMed, Wiley Cochrane Library.

Study Selection: Infants using long-term NIV outside an acute care setting.

Data Extraction: Study design, population characteristics, and NIV outcomes.

Results: A total of 289 studies were reviewed, with final inclusion of 52. Of these, 67% were retrospective; 98% quantitative; 92% single-center; and 48% were observational studies. Studies were distributed across upper airway (42%), neuromuscular (31%), central nervous system (8%), cardio-respiratory (2%), and multiple (17%) disease categories. While studies on upper airway disorders primarily reported changes in respiratory parameters (64%), studies on neuromuscular disease reported mortality (63%) and hospitalization (38%) outcomes.

Limitations: Most studies had an observational design with no control group, limiting the potential for a meta-analysis.

Conclusions: The outcomes reported in studies were reflective of the disease category being studied. Studies on upper airway conditions demonstrated improvements in respiratory parameters for infants using NIV. Studies on neuromuscular disease, which were almost exclusively on spinal muscular atrophy type 1, reported decreased hospitalizations and prolonged survival for infants. Overall, NIV is an effective long-term respiratory therapy for infants; however, the quality of the available evidence was low to very-low for all outcomes, limiting any strong conclusions.

2.2 INTRODUCTION

Long-term non-invasive ventilation (NIV), defined as respiratory support delivered through an interface outside the airway, has become the treatment of choice for a number of chronic conditions resulting in respiratory insufficiency or sleep disordered breathing in infants and children.[1-3] These conditions include upper airway disorders, neuromuscular disorders (NMD), and disorders of the central nervous system (CNS).[3-6] This shift towards NIV may be driven by improvements in NIV technology, a greater emphasis being placed on home-based care, and a growing acceptance of NIV as a viable therapy for long-term respiratory support.[1,6,7] With increasing numbers of infants and children living at home using NIV, understanding the benefits and risks of NIV is becoming important not only for specialists involved in starting this therapy but also for pediatricians and primary care physicians providing care to these children in the community.

While there is a considerable body of work describing the use of long-term NIV in a broad range of pediatric populations, less is known about its use in infants.[8-10] Without sufficient data to suggest otherwise, similar NIV treatment approaches are likely followed in both infants and older children, despite key physiological differences in sleep and breathing patterns in infancy. Both sleep and breathing processes are immature at birth and continue to develop through infancy, resulting in change in sleep patterns and breathing control that continue to change in early life.[11] Sleep occupies a greater proportion of time in infants compared to older children,[12] which makes infants more vulnerable to respiratory disorders that disrupt sleep. Immaturity of central respiratory centers in infants contributes to increased respiratory events (including central apneas and oxygen desaturations), and a greater variability in oxygen saturation, both of which

may be important for the normal development of respiratory control.[11,13] Since sleep and breathing processes differ by age, especially in early life, the type of respiratory and sleep disorders treated with NIV, the response to NIV treatment, and the outcomes for NIV may also differ in infants as compared to older children.

Most data available on long-term NIV use in infants is limited to single-center observational studies with relatively small sample sizes.[8] Aggregation of the available data for combined data analysis will improve our understanding of the risks and benefits of NIV therapy in the infant population. Therefore, the aim of this systematic review is to synthesize the characteristics, technology, and outcomes for infants using long-term NIV. The results of this systematic review will help inform clinicians and caregivers of the current level of evidence to support the use of NIV in the infant population, as well as identify gaps in knowledge to help guide future study.

2.3 METHODS

2.3.1 Protocol and Registration

The protocol for this systematic review was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[14] The full protocol has been registered in the PROSPERO database for international prospective reviews.[15]

2.3.2 Eligibility Criteria

The inclusion criteria for this systematic review were: (1) infants, defined by the Public Health Agency of Canada as ages 0-24 months inclusive;[16] (2) NIV use, defined as breathing support delivered from outside the airway; (3) long-term NIV use, defined as greater than three months

outside of an acute care setting. For studies that examined a broader age range, the mean age of NIV initiation had to be less than 24 months in order to be included in this review, or data had to be presented separately for infants. We did not place any study design or outcome level restrictions on eligibility.

2.3.3 Information Sources and Search

This systematic review is an extension of a prior scoping review on long-term NIV in children.[8] The scoping review search strategy, using Medical Subject Headings (MeSH) and free-text terms for "child" and "non-invasive ventilation," was developed for MEDLINE (Ovid) and adapted for subsequent electronic databases with the full protocol published elsewhere[17] (see Table 2.8 in Appendix I for original MEDLINE (Ovid) search strategy). Human studies published from 1990 onwards were searched in MEDLINE (Ovid), Embase (Ovid), CINAHL (Ebsco), Cochrane Library (Wiley), and PubMed between November 17-28, 2014, with no restriction on study design. Grey literature, in the form of conference abstracts on respiratory and sleep medicine, was identified from 2012-2014. The literature search was re-run on April 29, 2016 using the same search strategy in Ovid MEDLINE, Ovid Embase, CINAHL, PubMed and Wiley Cochrane Library to identify additional studies.

2.3.4 Study Selection

The titles and abstracts of English, French, Spanish, and Portuguese studies identified by the literature search were screened by two reviewers (JEM and MCC) to determine eligibility for full text retrieval. Studies that were considered eligible were full-text reviewed for inclusion by two reviewers (JEM and MCC). The final included studies pertaining to children 0-18 years were

then full-text screened by two reviewers (PKB and MMA) to identify studies relevant to infants for inclusion in this systematic review. Any disagreement at the screening, eligibility, and inclusion levels were discussed until a consensus was reached. The reference lists of studies meeting inclusion were also reviewed to identify any additional relevant literature.

2.3.5 Data Collection and Data Items

Data were entered into a pre-established data collection form in Microsoft Excel (version 14.0.4760, Microsoft Corporation, 2010). These data included author's name, year of publication, country of publication, study design, sample size, age of NIV initiation, NIV type, primary underlying disease conditions, co-morbidities, and primary and secondary outcome measures. One reviewer (PKB) extracted the data and 20% of data extraction was verified by a second reviewer (MCC).

Studies were grouped under one of the following primary underlying disease categories: upper airway disorders, NMD, CNS disorders, cardiorespiratory disorders, or multiple disorders. Within each disease category, we grouped studies based on individual disease conditions. We included studies with infants who had multiple disease conditions under one disease heading if >75% of the infant cohort had the same disease condition; otherwise these studies were included in the multiple disorders category.

2.3.6 Risk of Bias in Individual Studies

The Cochrane Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool[18] was used to assess the risk of bias in individual studies. Risk of bias in individual studies was

assessed by one reviewer (PKB) with 20% of the assessments verified by a second reviewer (JEM).

2.3.7 Quality Assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[19] was used to determine the quality of studies at an outcome level by one reviewer (PKB). Meta-analysis was performed to calculate risk ratios for appropriate outcomes using Review Manager (version 5.3., Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

2.3.8 Synthesis of Results

Primary and secondary outcomes were established during synthesis of the data based on outcomes reported in two or more studies for the same disease condition. Primary outcomes were objective changes in respiratory parameters, hospitalizations, discontinuation of NIV, and mortality. Secondary outcomes were adherence to respiratory support, improvements in underlying disease conditions, improvements in growth parameters, NIV facilitation of extubation, predictors of NIV requirement, and mask complications. Studies were included in the analysis if they reported on a primary and/or secondary outcome. Continuous infant data were presented as a weighted mean (standard deviation) or median (interquartile range) where appropriate. Results were grouped and reported based on the primary underlying disease category being studied. Primary outcomes were reported in tabular format if two or more studies reported on a primary outcome; otherwise they were reported narratively. Secondary outcomes were reported narratively if two or more studies examined the same secondary outcome.

2.4 RESULTS

2.4.1 Study Selection

The search strategy, after removal of duplicates, identified 11,581 studies and additional records (Figure 2.1). After screening of the titles and abstracts, 937 studies met eligibility for review. After full-text review, 289 studies on children ages 0-18 years were included in the scoping review. Full-text review of these 289 articles identified 56 studies meeting the infant inclusion criteria. Four conference proceedings met inclusion criteria, but were excluded because of insufficient data reporting, leaving 52 articles for inclusion in this systematic review (see Table 2.9 in Appendix I for characteristics and outcomes of all studies).

2.4.2 Study Characteristics and Outcomes

The majority of studies were retrospective (35/52, 67%), quantitative (51/52, 98%), and single-centre studies (48/52, 92%). The most common study design was observational, which included cohort studies (25/52, 48%), case series (13/52, 25%), and cross-sectional studies (6/52, 12%). Half of the studies (26/52, 50%) were exclusively on the infant population.

Based on primary underlying disease categories, the studies were distributed across upper airway disorders (21/52, 42%), NMD (16/52, 31%), CNS (4/52, 8%), cardiorespiratory diseases (1/52, 2%) and multiple disease categories (9/52, 17%; Table 2.1).

The reporting of primary outcomes in studies was as follows: changes in respiratory parameters (20/52, 38%), hospitalizations (8/52, 15%), NIV discontinuation (15/52, 29%) and mortality (13/52, 25%). Secondary outcomes reported by studies included improvements in growth

parameters (8/52, 15%), adherence (6/52, 12%), facilitation of extubation (5/52, 10%), predictors of NIV requirements (3/52, 6%), mask complications (2/52, 4%), and improvements in underlying conditions (1/52, 2%). Ten studies (10/52, 19%) only reported the number of infants using NIV, and did not report any infant NIV outcomes[7,20-28]; these studies were excluded from systematic review synthesis.

2.4.3 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) was the most common upper airway disorder studied in the infant population, with 12 studies (12/52, 23%) reporting on this condition (Table 2.1). Of these, 10 studies reported on infant NIV outcomes and were synthesized in the review (Table 2.2).[10,29-37] The studies reviewed included infants with multiple underlying conditions, the most common being a history of acute life-threatening events (ALTE), a family history of sudden infant death syndrome (SIDS), and craniofacial malformations. Eight studies (8/10, 80%) reported on changes in respiratory parameters,[10,29,31-36] with seven of these studies (7/10, 70%) reporting improvements in central, obstructive, and/or mixed apneas from a diagnostic to titration polysomnography.[10,29,31,32,34-36] Only one study (1/10, 10%) included diagnostic polysomnography results after long-term NIV use (weighted mean of 12 months), which showed overall decreased respiratory events, normalization of respiratory gases, and increased arousals during REM sleep.[36] Five studies (5/10, 50%) reported discontinuation of NIV in infants because of improvements in respiratory parameters, with discontinuation rates ranging from 14-100% (weighted mean 70±26%).[29,30,34,36,37] Only one study (1/10, 10%) on five infants using NIV reported mortality outcomes, with all infants alive at the time of study publication.[34] No studies reported on hospitalization outcomes.

2.4.4 Pierre Robin Sequence

The search strategy identified five studies (5/52, 10%) reporting on infants with Pierre Robin sequence (PRS) using long-term NIV (Table 2.1). Three studies (3/5, 60%) reported on primary and/or secondary outcomes and were synthesized for this review (Table 2.3).[38-40] A case series reported a decrease in respiratory rates, statistically significant improvements in respiratory effort, and normalization of respiratory gases after administration of NIV therapy in infants with PRS.[40] A cohort study reported normalization of polygraphy parameters and gas exchange post-NIV initiation.[38] Two studies on PRS reported on discontinuation from NIV in infants, with a combined 69% (11/16) of infants discontinuing NIV because of improvements in respiratory parameters.[38,40] Two studies comparing infants on NIV and invasive mechanical ventilation showed that the length of hospitalization were shorter for infants on NIV than for those receiving invasive mechanical ventilation via a tracheostomy.[38,39] Adherence of infants to NIV was reported as excellent, showing more than eight hours of NIV use per day in two studies,[38,40] with only a 1-2 week period required to adjust to the mask ventilation.[38,39] No studies addressed survival outcomes in infants with PRS using long-term NIV.

2.4.5 Laryngo-tracheomalacia

All four studies (4/52, 8%) on infants with laryngo-tracheomalacia (LTM) using long-term NIV were synthesized in the review (Table 2.4).[41-44] Three studies (3/4, 75%) reported on changes in respiratory parameters. A case-control study of 10 infants with LTM showed improvements in respiratory frequency and respiratory effort in infants using continuous positive airway pressure (CPAP) or bi-level ventilation (BPAP) compared to spontaneous breathing.[41] Normalization of arterial oxygen saturations after NIV use was seen in two studies.[44,45] NIV discontinuation due to

improvements in respiratory parameters was reported in two studies, with a combined discontinuation rate of 81% (13/16 infants).[43,45] Improvement in chest wall deformity after NIV use in three patients and normalization of growth parameters such as weight in four patients was seen in one case-control study.[45] The same study also reported an average NIV use per day of 10.2 hours/day in 7 infants.

2.4.6 Spinal Muscular Atrophy Type 1

There were 14 studies (14/52, 27%) of infants with spinal muscular atrophy type 1 (SMA1) using long-term NIV (Table 2.1). Twelve of these studies reported on primary and/or secondary outcomes and were synthesized (Table 2.5).[47-58] Nine studies (9/12, 75%) reported on mortality outcomes[47,49-52,54-56,58]; four of these studies compared infants on supportive care with those using NIV, showing prolonged survival in the NIV group.[47,50,54,55] Six studies (6/12, 50%) reported outcomes on hospitalization outcomes.[47,49,50,54-56] Of these, two studies reported that hospitalizations per patient per year were significantly higher in infants on NIV than infants with a tracheostomy until after three years of age.[47,50] Three studies (3/12, 25%) reported improvements in growth parameters, seen by resolution of chest wall deformity (pectus excavatum) after the initiation of NIV therapy.[48,49,52] Another three studies showed that NIV helped facilitate extubation in infants with SMA1.[49,51,53] Only one study (1/12, 8%) reported on changes in respiratory parameters and showed improvements in respiratory effort and normalization of respiratory gases in SMA1 patients using NIV therapy.[50]

2.4.7 Central Hypoventilation Syndrome

There were four studies (4/52, 8%) on NIV use for infants with central hypoventilation syndrome (CHS), and all four were summarized (Table 2.6).[59-62] The diagnosis of CHS was confirmed clinically in two studies[58,60] and via PHOX2B gene mutation analysis in one study.[59] NIV was used in conjunction with negative extra-thoracic pressure ventilation (VNEP) therapy in two studies[58-60]: in one study it was used as the primary therapy, and in the second study, CPAP was used to relieve upper airway obstruction not resolved with VNEP. Improvements in respiratory parameters were reported in two studies: one showed the normalization of the partial pressure of carbon dioxide and resolution of pulmonary hypertension following the use of NIV[62] and the other study showed improvements in hypoventilation of 50% (3/6) of infants.[59] One study with six infants reported NIV discontinuation in two infants (33%) because of improvements in respiratory parameters; the remaining four infants were using NIV only during sleep.[58] Two studies showed parent-reported improvements in growth and development after NIV initiation using the results of a parent questionnaire.[59,60] An additional two studies reported pressure related effects of mask use, which were predominantly skin breakdown and mid-face hypoplasia.[61,62] One cross-sectional study showed that it took less than a week for 5 of 6 infants to adjust to NIV.[59]

2.4.8 Synthesis of results

The results of meta-analysis on the effect of NIV on mortality rates in infants with SMA1 showed that there was a statistically significant decrease in the relative risk of mortality in the NIV group compared to the supportive care group (Figure 2.2). This decrease may be attributed to prolonged survival in infants using NIV.

2.4.9 Risk of bias and quality assessment of outcomes

Risk of bias, determined by the Cochrane ROBINS-I tool, ranged from moderate to severe in all studies included in this review (see Table 2.10 in Appendix I). Study design was the main contributor to the low quality assessment of the studies. Almost all the included studies had an observational study design, which contributed to confounding bias in participant selection and selected reporting of results. Grading of the quality of the evidence for outcomes such as changes in respiratory parameters, hospitalization, survival, and adherence using GRADE methodology showed that the quality of evidence ranged from low to very-low for all studies (Table 2.7).

2.5 DISCUSSION

2.5.1 Summary of evidence

To our knowledge, this is the first systematic review on the use of NIV in infants. We identified studies on a diverse range of upper airway conditions in which NIV therapy improved the results of polysomnographic and respiratory parameters. With data available for NMD and CNS disorders limited to SMA1 and CHS, extrapolation of NIV benefits to other NMD and CNS disorders in infants is challenging. Not all outcomes were studied in all disease categories, with hospitalizations and mortality the focus in studies of SMA, respiratory events, and length of hospitalization in studies of PRS, and respiratory events and discontinuation in the remaining groups. The overall quality of evidence to support appropriate conclusions was low to very-low for all studies in this review.

There is a diverse range of upper airway disorders that may benefit from NIV therapy. Previous studies have identified a number of conditions that can predispose infants to upper airway

obstruction, including craniofacial disorders, laryngeal disorders, and nasal obstruction.[66] Similarly in this review, we identified NIV use in a wide variety of diseases associated with compromised upper airway function, the most common being OSA, PRS, ALTE, infants at risk for SIDS, and LTM. The improvement in respiratory parameters and NIV discontinuation with respect to disease condition reflected an overall benefit from NIV therapy in infants with UA disorders. Extrapolating these results to conditions with a similar pathophysiology, but for which there is no evidence for NIV use in the literature, may be reasonable given the diversity of disorders represented in the available evidence.

By contrast, extrapolation of outcomes for long-term NIV use in NMD and CNS disorders may be more challenging. The data relevant to long-term NIV use for NMD and CNS disorders is almost exclusively from two conditions: SMA1 and CHS. SMA1 is a progressively deteriorating disorder that is usually fatal in infancy. This is in contrast to other NMD disorders presenting in infancy, such as congenital myopathy and congenital muscular dystrophy, which may have a better prognosis or steadier course.[7,66] The difference in prognoses of these conditions makes generalizing outcomes for NIV use in SMA1 to other NMD less appropriate. Similarly, CHS was the only CNS disorder for which data on long-term NIV use was available. NIV may be useful for other CNS disorders with accompanying respiratory compromise, such as congenital or acquired brain injury. Given the potentially unique physiology of CHS extrapolating the outcomes of NIV use for infants with CHS to other CNS conditions with different underlying respiratory pathophysiology may not be appropriate. Creation of national disease registries for infants and children using NIV will provide the opportunity to aggregate data on rare or

minimally studied diseases and examine the use and outcomes of long-term NIV in these populations.

The outcomes that were reported in studies differed depending on the primary underlying disease category that was being examined. Studies of upper airway conditions predominantly reported on changes in respiratory parameters reported via polysomnography results and discontinuation of NIV. In addition, most studies reported short-term overnight polysomnography results; only one study had data on polysomnography results after long-term follow-up periods of NIV use in infants.[33] Only one upper airway study reported on mortality outcomes and none on hospitalization outcomes. Long-term outcomes, such as hospitalizations, intercurrent illness, growth and development, and quality of life, which may be of interest to parents and caregivers warrant further studying. Interestingly, studies on SMA1 predominantly reported on mortality and hospitalization outcomes, with only one study reporting on changes in respiratory parameters.

While the overall quality of the evidence available for the use of long-term NIV in infants may be low to very low, there is a body of evidence that may help guide clinical practice. In the absence of clear strong evidence, it is reasonable to use the information available where appropriate, even if it is limited. The reason for the low quality of the evidence included the study design and a high risk of bias due to the lack of blinding and randomization, and control for confounding variables. While these findings highlight the need for future studies of strong design and lower risk of bias, such as prospective studies with a larger sample size and

controlled for confounding variables, the data which is currently available may still be useful to inform treatment decisions for conditions where long-term NIV is being considered.

2.5.2 Limitations of the Included Studies

We identified a number of research gaps present in the studies included within this review. There was only one study that compared the efficacy of CPAP and BPAP ventilation in a cohort of infants.[41] Similarly, while some studies reported mask complications[9,30], only one compared the efficacy and practicality of different infant NIV masks.[27] Additionally, there were no studies on the clinical support networks necessary for infants to be placed on NIV. It is important to know whether infants receive consultation and support from physicians, registered nurses, home care support, or a combination thereof, in order to determine whether a multidisciplinary NIV care plan is necessary for this population. The lack of comparison groups and/or homogeneity of outcomes reported precluded meta-analysis for most topics.

2.5.3 Limitations of the Review

Our review relied on the search methods and primary-level screening decisions of a scoping review on NIV in children with subsequent development of the research questions on NIV in infants. The methods to identify studies for the scoping review, however, were sufficiently inclusive to capture all relevant evidence on NIV in infants. We defined NIV for the scoping review on long-term NIV as breathing support outside the airway via an interface, consistent with the MeSH terminology for NIV and, therefore, included CPAP as well as BPAP. Some investigators, however, do not consider CPAP as a mode of NIV because it requires spontaneous breathing from the patient.[1,67] To address this concern, we reported the different ventilation types

used by infants in the tables included in this review. Finally, we defined infants as ages 0-2 years based on the Public Health Agency of Canada definition.[16] Some investigators may not agree with this definition, as the Centre for Disease Control defines infants as less than one year of age. Regardless of the definition used, it is still unclear whether there are differences in the outcomes of infants on NIV with respect to age. Future work should consider whether infants represent a distinct group within children using long-term NIV.

2.6 CONCLUSIONS

This systematic review examines the use and outcomes of long-term NIV in infants with a range of respiratory and sleep disorders. Improvements in respiratory parameters and discontinuation from NIV due to improvement in underlying conditions have been shown for a broad range of upper airway disorders, such as OSA, PRS, and LTM, in infants. Long-term NIV use in infants with SMA1 decreased hospitalizations and prolonged survival compared to infants on supportive care. Infants with CHS may also show improvements in respiratory parameters after using NIV, and may potentially avoid tracheostomy. NIV appears to be a feasible method of providing long-term respiratory support for infants with a wide range of underlying conditions; however, several methodological weaknesses limit any strong categorical conclusions. The findings of this systematic review are relevant to a broad range of stakeholders and can be used to help guide clinicians on the use of long-term NIV in infants.

ACKNOWLEDGEMENTS

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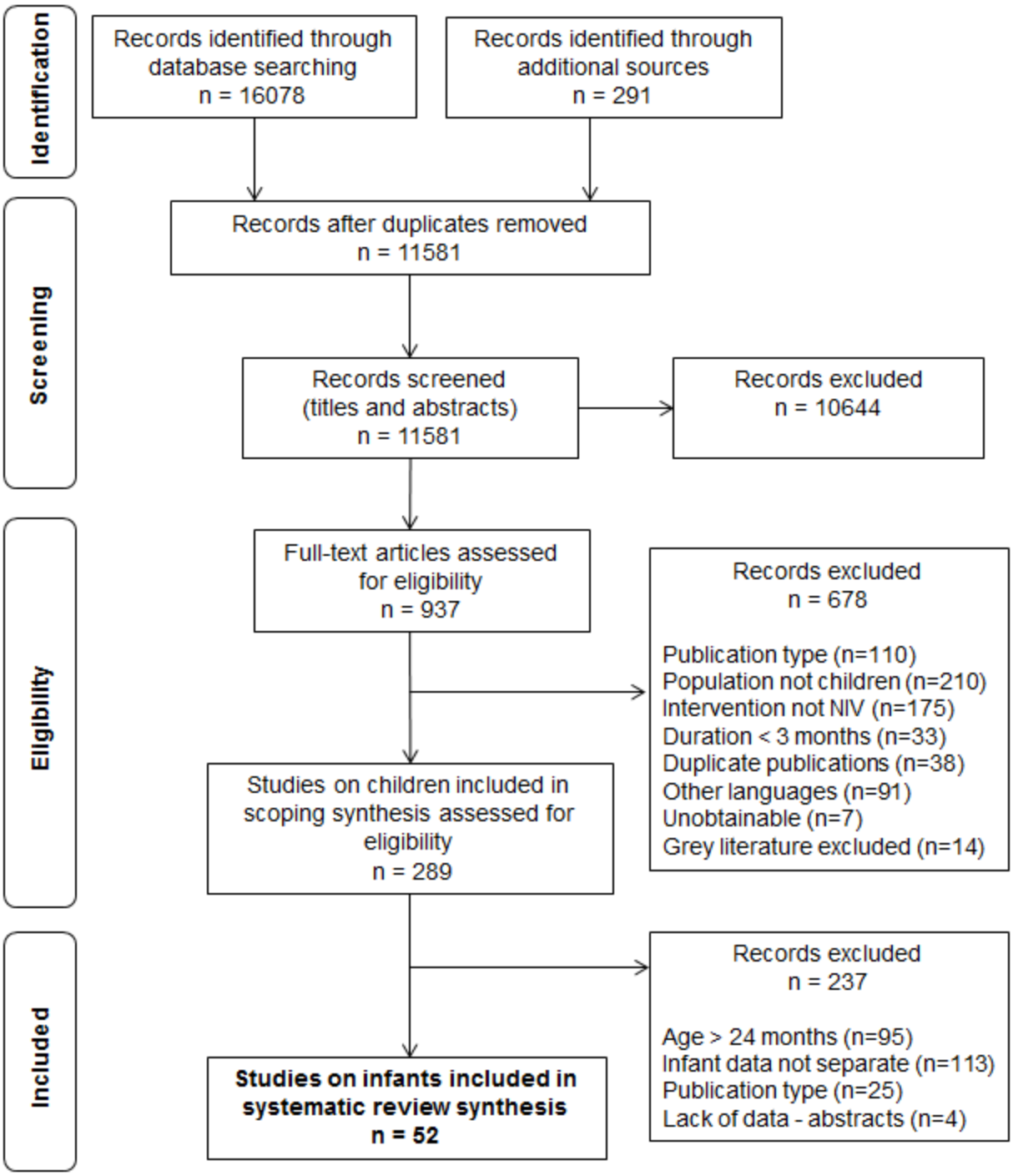

Figure 2.1: Flow diagram outlining the study selection process for the systematic review, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10]

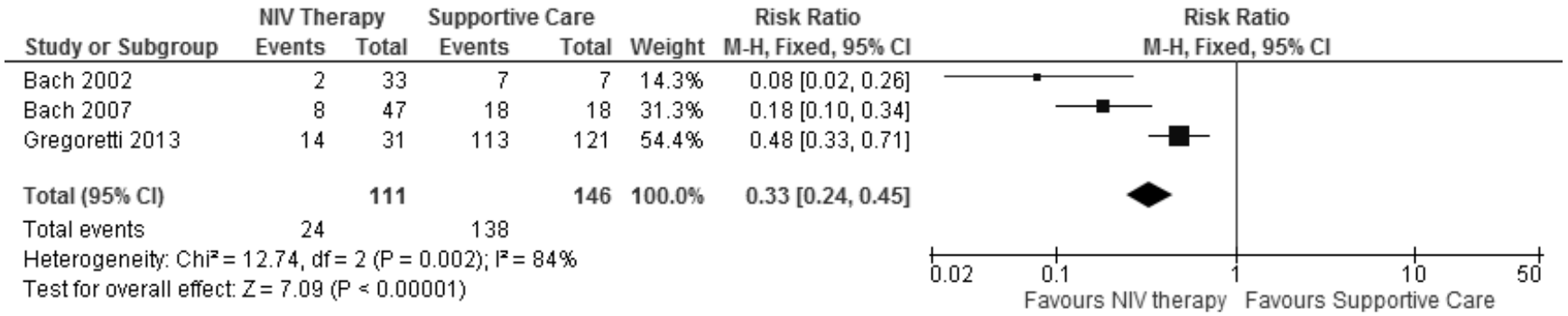

Figure 2.2: A meta-analysis on the effect of non-invasive ventilation (NIV) on the relative risk of mortality in infants with spinal muscular atrophy. The meta-analysis shows that the relative risk of mortality is significantly lower in infants using NIV compared infants on supportive care. This decrease may be attributed to prolonged survival in infants using long-term NIV compared to no therapy.

Table 2.1: Summary of characteristics and outcomes of studies on infants using long-term non-invasive ventilation by disease category.

Primary underlying disease category	Specific disease/condition studied	# of articles	Reference number(s)	Infant outcome measures reported by number of articles (n)
Upper airway	Obstructive Sleep Apnea	12	[10, 25-26, 29-37]	▪ Changes in respiratory parameters (n=8) ▪ Discontinuation of NIV (n=5) ▪ Benefit of NIV – improvement in growth parameters (n=1) ▪ Survival/mortality (n=1) ▪ No outcome (only number of infants using NIV, n=2)
	Pierre Robin Sequence	5	[22-23, 38-40]	▪ Changes in respiratory parameters (n=2) ▪ Hospitalization (n=2) ▪ Discontinuation of NIV (n=2) ▪ Adherence to NIV (n=2) ▪ No outcome (only number of infants using NIV, n=2)
	Laryngo-tracheomalacia	4	[41-44]	▪ Changes in respiratory parameters (n=3) ▪ Discontinuation of NIV (n=2) ▪ Benefit of NIV – improvement in growth parameters (n=1) ▪ Benefit of NIV – improvement in underlying condition (n=1) ▪ Adherence to NIV (n=1)
	Breath holding spells	1	[68]	▪ Changes in respiratory parameters (n=1)
Neuromuscular	Spinal Muscular Atrophy	14	[21, 24, 47-58]	▪ Survival/mortality (n=9) ▪ Hospitalization (n=6) ▪ Benefit of NIV – improvement in growth parameters (n=3) ▪ Benefit of NIV – extubation (n=3) ▪ Changes in respiratory parameters (n=1) ▪ No outcome (only number of infants using NIV, n=2)
	Multiple neuromuscular conditions	1	[66]	▪ Survival/mortality (n=1)
	Achondroplasia	1	[20]	▪ No outcome (only number of infants using NIV, n=1)

Central Nervous System	Central Hypoventilation Syndrome	4	[59-62]	▪ Changes in respiratory parameters (n=2) ▪ Discontinuation of NIV (n=2) ▪ Benefit of NIV – improvements in growth parameters (n=2) ▪ Benefit of NIV – extubation (n=2) ▪ Mask complications (n=2) ▪ Adherence to NIV (n=1)
Cardiorespiratory	Congenital Heart Disease	1	[63]	▪ Changes in respiratory parameters, discontinuation of NIV (n=1)
Multiple	Multiple	9	[3, 7, 9, 27-28, 64-65, 69]	▪ Discontinuation of ventilation (n=3) ▪ Changes in respiratory parameters (n=2) ▪ Survival/mortality (n=2) ▪ Adherence to NIV (n=2) ▪ No outcome (only number of infants using NIV, n=3)

NIV - non-invasive ventilation; QOL – quality of life

Table 2.2: Summary of studies on infants with obstructive sleep apnea using long-term non-invasive ventilation.

First author Year Country	Study design	OSA definition; Diagnosis	Infants using NIV	Age	Medical history of conditions/ syndromes	NIV type	Improvement in respiratory parameters (events/hour unless otherwise specified)			Infants who discontinued NIV (n, %)
							Variables	Pre-NIV[a] mean±SD	Post-NIV mean±SD	
Harrington[31] 2003 Australia, Finland	P, Obs: Case-control	n/a Apnea: cessation of airflow > 2 respiratory cycles Diagnosis: PSG	n=6	13±4 wk	ALTE (n=4); FHx SIDS (n=2)	CPAP	Obstructive index[b]* Oxygen desaturations (%)** Arousal in NREM sleep (%) Arousal in REM sleep (%)** HR in NREM sleep (bpm)* HR in REM sleep (bpm)* HRV in NREM sleep (%)* HRV in REM sleep (%)	17±6 12±3 20±23 19±19 131±9 137±9 2.4±0.8 3.0±1.2	1±1 2±1 19±19 68±11 118±5 124±5 4.5±1.7 4.1±1.6	n/a
Downey[29] 2000 USA	R, Obs: Cohort	> 1 obstructive apnea events/hour of sleep Diagnosis: PSG	n=18[c]	< 2 yr	ALTE (n=1); DS (n=1); LTM (n=3); PRS (n=1); BPD (n=1); CHF (n=1); Post T&A (n=2)[c]	CPAP	Total apnea index† Obstructive apnea index† Hypopnea apnea index* Oxygen saturation < 90% (min)*	12.8±20.0 4.7±13.4 6.7±12.7 22.2±25.5	4.5±13.4 2.0±7.3 2.0±5.7 6.4±14.9	(n=9, 90%) discontinued because of improvement in respiratory parameters.
McNamara[34] 1995 Australia	P, Control before-after	n/a Apnea: cessation of airflow > 2 sec Diagnosis: PSG	n=5[d]	8-12 wk	ALTE (n=1); FHx SIDS (n=4)	CPAP	Total apnea index in NREM sleep** Total apnea index in REM sleep** Central index in NREM sleep** Central index in REM sleep Obstructive index[e] in NREM sleep** Obstructive index[e] in REM sleep** REM sleep per total sleep time (%)**	65.6±14.6 106.1±13.9 36.5±6.6 25.6±4.5 29.3±9.4 80.8±16.8 14.2±1.2	10.5±14.6 26.6±13.9 10.3±6.6 24.6±4.5 0.3±9.4 2.0±16.8 27.1±1.2	(n=3, 100%) discontinued after 2-5 mo because of improvement in respiratory parameters.
McNamara[36] 1999 Australia	P, Obs: Cohort	> 5 mixed & obstructive apneas events/hour of sleep Diagnosis: PSG (n=21); overnight ambulatory study (n=3)	n=24[f]	1-51 wk	ALTE (n = 8); FHx SIDS(n=5); CF anomalies (n=7); LTM (n=1); Syndromes (n=3)	CPAP	Total apnea index in NREM sleep* Total apnea index in REM sleep* Central apneas in NREM sleep* Central apneas in REM sleep Obstructive apneas in NREM sleep* Obstructive apneas in REM sleep* Desaturation index in NREM sleep* Desaturation index in REM sleep* REM sleep per total sleep time (%)*	44.4±9.3 68.6±8.9 29.8±7.6 25.0±4.3 14.6±3.9 43.6±8.3 37.8±8.9 63.4±8.5 16.0±1.2	9.5±1.2 22.7±2.3 9.4±1.2 22.3±2.2 0.1±0.1 0.4±0.1 4.1±0.9 9.8±1.4 28.8±0.9	(n=13, 72%) discontinued because of improvements in respiratory parameters.[g]

McNamara[35] 1999 Australia	P, Obs: Case-control	> 5 obstructive events/hour of sleep Diagnosis: PSG	n=8	10.8±1.3 wk	ALTE; FHx SIDS	CPAP	NREM Sleep Central apneas in NREM sleep Obstructive apneas in NREM sleep* Central apneas in REM sleep Obstructive apneas in REM sleep*	 36.1±8.6 22.2±8.8 32.9±8.1 54.8±16.3	 26.3±7.4 10.6±2.6 38.2±8.2 25.7±7.2	n/a
Leonardis[32] 2013 USA	R, Obs: Cohort	AHI ≥ 1.5 events/hour of sleep Diagnosis: PSG	n=18	Mean: 16.0 mo	Multiple conditions/ syndromes[h]	CPAP BPAP	Mean percent decrease in AHI (%)[i] Subjective efficacy (-1 to 3 scale)[j]	67.2 2.2		n/a
Robison[10] 2013 USA	R, Obs: Cohort	AHI ≥ 1.5 events/hour of sleep Diagnosis: PSG	n=18	Mean: 15.6 mo (3-29mo)	Multiple conditions/ syndromes[k]	CPAP BPAP	Mean percent decrease in AHI (%)[i] Subjective efficacy (-1 to 3 scale)[j]	84.1 2.5		n/a
Liu[33] 2012 China	R; Obs: Case series		n=2	1 – 7 mo	PRS (n=1); LTM (n=1)	CPAP (n=1) BPAP (n=1)	Normalization of respiratory gases			
Guilleminault[30] 1995 USA	P, Obs: Case-control	AHI > 1 to 5 events/hour of sleep (use SDB in text) Diagnosis: PSG	n=72	Mean: 24±9 wk (4-43mo)	ALTE (n=14); DS (n=7); CF anomalies (n=17); neurological disorders (n=14)	CPAP	n/a			(n=10, 14%) discontinued ventilation because of improvements in respiratory parameters.[l]
Rosen[37] 2010 United States	R, Obs: Cohort	AHI > 1 event/hour Diagnosis: PSG	n=6	< 2 yr	Down syndrome (n=6)	CPAP	n/a			(n=3, 50%) discontinued after 5-10 mo because of improvements in respiratory parameters.

AHI - apnea-hypopnea index; ALTE - apparent life-threatening event; BPAP – bi-level positive airway pressure; BPD - bronchopulmonary dysplasia; bpm – beats per minute; CF - craniofacial; CHF - congestive heart failure; CPAP - continuous positive airway pressure; DS - Down Syndrome; FHx – Family history; f/up - follow-up; HR – heart rate; HRV – heart rate variability; LTM - laryngo-tracheomalacia; mo – months; n/a – data not reported; NIV - non-invasive ventilation; NREM - non-rapid eye movement; obs - observational; OSA - obstructive sleep apnea; P - prospective; PRS - Pierre Robin Sequence; PSG - polysomnography; R - retrospective; REM - rapid eye movement; SIDS - sudden infant death syndrome; T&A - tonsillectomy and adenoidectomy; wk – weeks; yr - years

*p<0.05, **p<0.01, +p<0.001

[a] Pre-NIV refers to results on a diagnostic PSG; post-NIV refers to a next-day f/up titration study.
[b] Reported in the study as the obstructive respiratory disturbance index, and was defined as the sum of the obstructive apneas, mixed apneas, and obstructive hypopneas per hour of sleep.
[c] Only 10/18 used NIV long-term (1 – 5 yr).
[d] Only 3/5 used NIV long-term (from 2 – 5 mo).
[e] Refers to both obstructive and mixed apneas.
[f] Only 18/24 used NIV long-term (from 1 mo to 4 yr).
[g] Of the 13 infants who discontinued NIV, 11 had a history of ALTE or family history of SIDS, 1 had choanal atresia, and 1 had a vascular ring that was corrected surgically. The 5 infants who still require NIV all have an upper airway anatomical abnormality as part of their primary underlying diagnosis.
[h] Multiple syndromes/conditions reported are reported for entire population; not specific to NIV population. These include Down syndrome (n=10), cleft palate (n=9), Pierre Robin sequence (n=6), achondroplasia (n=6), Skeletal dysplasia (n=3), and other syndromes (n=9).
[i] Mean percent decrease in AHI (%) shown from pre- to post-NIV therapy.
[j] Subjective improvement defined as: -1 worsening of symptoms; 0 no improvement; +1 mild improvement; +2 moderate improvement; +3 significant improvements/resolution.
[k] Multiple syndromes/conditions reported are reported for entire population; not specific to NIV population. These include Down syndrome (n=14), Prader-Willi syndrome (n=5), Di-George syndrome (n=3), VACTERL (n=3), and other syndromes (n=13).
[l] A total of 28 infants discontinued long-term NIV: 10 infants discontinued because of improvements in respiratory parameters; 18 required T&A or were referred to orthodontics. The mean f/up duration was 35±21 mo.

Table 2.3: Summary of studies of infants with Pierre Robin sequence using long-term non-invasive ventilation.

First author Year Country	Study design	Infants using NIV	Age	NIV type	Improvement in respiratory parameters (events/hour unless otherwise stated)			Infants who discontinued ventilation (n, %)	Length of hospital stay (mean±SD or median (range))		
					Variable(s)	Pre-NIV mean±SD	Post-NIV mean±SD		Supportive Care Group	NIV Group	IMV Group[a]
Leboulanger[40] 2010 France	P; Obs: Case Series	n=7	Median: 2 mo (1-10mo)	CPAP (n=5) BPAP (n=2)	RR (breaths/min) T_I/T_{TOT}(%)* P_{es} swing (cm H_2O)* P_{di} swing (cm H_2O)* % time S_pO_2 < 90%* % time $P_{tc}CO_2$ >50mmHg† Mean $P_{tc}CO_2$*	55±9 59±9 29±13 31±12 14±10 88±12 57±7	37±7 40±7 9±4 12±5 1±2 0±0 31±7	(n=5, 71%) discontinued NIV after a mean 16.7±12.2 mo due to improvements in respiratory parameters.	n/a	n/a	n/a
Amaddeo[28] 2016 France	R; Obs: Cohort	n=9	0-2 mo	CPAP	Apnea-hypopnea index Oxygen desaturation index Minimum S_pO_2 (%) % time S_pO_2 < 90% Maximum $P_{tc}CO_2$ (%)	19-42 18-137 78-90 0-16 41-55	Normal PG and/or gas exchange[b]	(n=6, 66%) discontinued due to improvements in respiratory parameters.	n/a	1 mo (20-40d)	2 mo (6wk - 4mo)
Kam[39] 2015 Canada	R; Obs: Cohort	n=20	Mean: 23 mo (5d - 8yr)	CPAP	n/a	n/a		n/a	28±24 d	66±46 d	138±76 d†

BPAP – bi-level positive airway pressure; CPAP – continuous positive airway pressure; d – days; IMV – invasive mechanical ventilation; mo – months; n/a – data not reported or applicable; NIV- non-invasive ventilation; Obs – observational; P- prospective; $P_{tc}CO_2$ – partial pressure of transcutaneous carbon dioxide; Pdi –diaphragmatic pressure; P_{es} – esophageal pressure; PG – polygraphy; R- retrospective; RR – respiratory rate; SpO_2 – partial pressure of oxygen; T_I/T_{TOT} –inspiratory time (T_I)/total respiratory cycle time(T_{TOT}); wk – weeks; yr - years

*p<0.05; **p<0.01; †p<0.001

[a] Invasive mechanical ventilation (IMV) delivered via tracheostomy.
[b] Study reports that criteria for CPAP withdrawl in 6 infants was "normal polygraphy" (n=2) and/or "normal gas exchange" (n=6), but actual respiratory values are not provided.

Table 2.4: Summary of studies on infants with laryno-tracheomalacia using long-term non-invasive ventilation.

First author Year Country	Study design	Infants using NIV	Age	NIV type	Improvement in respiratory parameters (mean±SD or median (range))				Infants who discontinued NIV (n, %)
					Variables	Supportive Care	CPAP	Bi-level	
Essouri[41] 2005, France	P; Obs: Case-control	n=10[a]	Median: 9.5 mo (3-18 mo)	CPAP (n=10) BPAP (n=10) [b]	RR (breaths/min) T_I/T_{TOT} (%) P_{es} swing (cm H_2O) P_{di} swing (cm H_2O) PTP_{es}/min ($cmH_2O\ s^{-1}\ min^{-1}$) PTP_{di}/min ($cmH_2O\ s^{-1}\ min^{-1}$)	45 (24-84) 63 (35-86) 28 (13-76) 30 (16-75) 695 (364-1417) 845 (159-1183)	29 (18-60) 41 (34-60)** 10 (7-28)** 12 (8-32)** 143 (98-469)** 195 (115-434)**	25 (14-50)**[c] 48 (28-55)** 13 (6-33)** 14 (7-33)** 211 (73-588)** 248 (45-784)**	n/a
Fauroux[42] 2001, France, UK	P; Obs: Case-control	n=5	Overall: 32.9±25.8 mo [d] Infants: 8-19 mo	CPAP	S_aO_2 (%)* S_aO_2 nadir (%)* % sleep with S_aO_2 < 90%*	91.7±2.3 74.7±7.5 29.5±19.6	96.2±2.0 88.0±2.5 0.5±0.8	n/a	(n=3, 60%) discontinued NIV after 6 – 30 mo due to improvements in respiratory parameters.
Zwacka[44] 1997, Germany	R: Obs: Cohort	n=7	3 wk – 3 mo	CPAP	HR (beats/min)[e] RR (breaths/min) S_aO_2 in REM sleep (%) S_aO_2 in NREM sleep (%)	135-160 34-42 60-95 85-98	110-130 22-28 88-100 92-100	n/a	n/a
Shatz[43] 2004, Israel	R; Obs: Cohort	n=14[f]	Mean: 6.5±3.5 mo (1-18 mo)[g]	CPAP (n=5) BPAP (n=9)	n/a				(n=9, 100%) on bi-level discontinued by 3 years of age due to improvement in respiratory parameters.[h]

BPAP – bi-level positive airway pressure; CPAP - continuous positive airway pressure; HR – heart rate; LTM – laryngo-tracheomalacia; mo – months; n/a – data not reported or applicable; NIV - non-invasive ventilation; NREM – non-rapid eye movement; Obs – observational; P – prospective; P_{di} – diaphragmatic pressure; P_{es} – esophageal pressure; PTP_{di} diaphragmatic pressure-time product; PTP_{es} esophageal pressure-time product; R- retrospective; REM – rapid eye movement; RR – respiratory rate; S_aO_2 – partial pressure of oxygen; T_I/T_{TOT} – inspiratory time (T_I)/total respiratory cycle time(T_{TOT}); TST – total sleep time; wk - weeks

*p<0.05; **p<0.01

[a] 8 of 10 (80%) infants had LTM.
[b] All 10 infants were put on both CPAP and BPAP ventilation to compare the two types of ventilation.
[c] Reporting of significant difference is between spontaneous breathing and CPAP or BPAP group respectively. No significant differences between CPAP group and BPAP group.
[d] Cohort had 12 subjects split into group 1 (n=5) and group 2 (n=7). Since data were reported separately for each group, only group 2 data are presented in the table because it is more representative of the infant population (mean age < 24 months for group 2).
[e] Statistics not reported; a significant decrease in heart rate and respiratory rate, self-regulating respiratory patterns, and normalization of respiratory gases is mentioned in the text.
[f] Entire cohort consisted of 50 infants. 39/50 (78%) of infants had LTM; 18/50 (36%) of infants had tracheomalacia. The number of infants with combined laryngomalacia and tracheomalacia was not reported.

[g] Age for overall infant group, not just those on NIV.
[h] Discontinuation of infants on CPAP was not reported.

Table 2.5: Summary of studies on long-term non-invasive ventilation in infants with spinal muscular atrophy (SMA) type 1.

First Author Year Country	Study Design	Age	Infants on NIV	NIV type	Mortality (n/group N, % unless otherwise specified)				Hospitalization (per patient/year unless otherwise specified)			
					Variable(s)	Supportive care group	NIV group	IMV group	Variables	Supportive care group	NIV group	IMV group
Bach[46] 2002 USA	R; Obs: Case series	11.2±5.7 mo	n=33	BPAP	Number of deaths	7/7, 100	2/33, 6	1/16, 6	Ages 0-3 yr* Ages > 3 yr	n/a n/a	1.53 0.20	0.58 0.21
Bach[49] 2007 USA	R; Obs: Cohort	10.6±5.7 mo	n=47	BPAP	Number of deaths	18/18, 100	8/47, 17	5/27, 19	Ages 0-3 yr† Ages > 5 yr*	n/a n/a	1.58 0.04	0.37 0.13
Gregoretti[53] 2013 Italy	R; Obs: Case series	12.6±14.4 mo	n=31	BPAP	Number of deaths % survival at 24 mo† % survival at 48 mo†	113/121, 93 n/a n/a	14/31, 45 89.43 45	7/42, 17 95 67.7	Hospitalization	n/a	0.023	0.006
Lemoine[54] 2012 USA	R; Obs: Cohort	Mean: 136d[b] (54 –196)	n=26	BPAP	Number of deaths	NIV group had statistically longer survival compared to the supportive care group (log rank 0.047).			Hospitalization rate (%)	46	83	n/a
Ottonello[55] 2011 Italy	R; Obs: Cohort	10.4±6.2 mo	n=16	BPAP	Number of deaths	n/a	2/16, 13	n/a	Hospitalization	n/a	0.15	n/a
						NIV Group				NIV Group		
Bach[48] 2000 USA	R; Obs: Case series	3-28 mo	n=8	BPAP	Number of deaths	1/8, 13			Hospitalization duration (d)[a]	16.6±7.8		
Birnkrant[50] 1998 USA	R; Obs: Case series	4 – 9mo	n=3	BPAP	Number of deaths	4/4, 100[b]			Hospitalization	n/a		
Chatwin[51] 2011 UK	R; Obs: Cohort	Median: 11 mo (4-24 mo)	n=13[c]	BPAP	Number of deaths	5/13, 38			Hospitalization	n/a		
Vasconcelos[57] 2005 Portugal	R; Obs: Cohort	13 mo (3mo-3yr)	n=7	BPAP	Number of deaths	5/7, 71[d]			Hospitalization	n/a		

BPAP – bi-level positive airway pressure; d – days; IMV – invasive mechanical ventilation; mo – months; N – number; NA – not applicable; n/a – data not reported or applicable; NIV – non-invasive ventilation; Obs – observational study; P – prospective; R – retrospective; SMA – spinal muscular atrophy; Tx – treatment; yr - years

*p<0.05; **p<0.01; †p<0.001

[a] Reported for only one centre.

[b] Infants died 1-3.5 mo after severe aspirations due to complications of the underlying disease condition.

[c] 2/13 infants had borderline type I/II spinal muscular atrophy.

[d] 5/7 infants died 1-15 mo after starting NIV therapy due to complications of the underlying disease condition.

Table 2.6: Summary of studies on infants with central hypoventilation syndrome using long-term non-invasive ventilation.

First Author Year Country	Study design	Diagnosis of CHS	Infants on NIV	Age	NIV type	Improvement in respiratory parameters	Infants who discontinued NIV (n, %)
Tibballs[61] 2003 Australia	R; Obs: Case series	Clinical via polysomnography	n=2	6 wk and 9 mo	BPAP (n=2) VNEP[a] (n=2)	Decrease in P_aCO_2 to 40-50mmHg (n=1) Normalization of pulmonary hypertension (n=1)	n/a
Hartmann[58] 1994 UK	P; Obs: Case series	Clinical via respiratory gases and plethysmography	n=6	Overall: 22 d – 57 mo Infants: 22d – 5 mo	VNEP (n=6) CPAP (n=2)[b]	Improvements in hypoventilation (n=3)[c]	(n=2, 33%) discontinued because of improvements in respiratory parameters.
Noyes[59] 1999	P; Obs: Cross-sectional (with content analysis)	n/a	n=5	66d – 59 mo	VNEP (n=5) CPAP (n=1)[d]		discontinuation
Ramesh[60] 2008 UK	P; Obs: Cross-sectional	Genetic via PHOX2B gene mutation and clinical via polysomnography	n=6	Median: 8 wk (5 – 26 wk)	n/a	n/a	(n=0, 0%) discontinued ventilation at the conclusion of the study.

BPAP – bi-level positive airway pressure; CHS – central hypoventilation syndrome; CPAP – continuous positive airway pressure; d – days; mo – months;NIV – non-invasive ventilation; n/a – data not reported; Obs – observational study; P – prospective; P_aCO_2 – partial pressure of carbon dioxide; PHT – pulmonary hypertension; R – retrospective; VNEP – negative extrathoracic pressure ventilation; wk - weeks

[a] VNEP was used in conjunction with BPAP to relieve mask complications.
[b] CPAP was used in conjunction with VNEP in two infants to relieve upper airway obstruction.
[c] Study reported that three infants had improvements in hypoventilation, but did not report respiratory values.
[d] CPAP used in conjunction with VNEP in one infant.

Table 2.7: Quality assessment of outcomes of infants using long-term non-invasive ventilation using the GRADE criteria.[19]

Quality assessment							Number of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Obstructive sleep apnea												
Changes in respiratory parameters: (respiratory gases pre-NIV to post-NIV)												
5	observational studies	serious	not serious	not serious	not serious	none	53	53			⨁⨁◯◯ LOW	Important
3[c]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Discontinuation of NIV:												
5[d]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁⨁◯◯ LOW	Important
Pierre Robin Sequence												
Changes in respiratory parameters: (respiratory gases pre-NIV to post-NIV)												
2[e]	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Discontinuation of NIV:												
2[f]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Length of hospitalization:												
2[g]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Adherence:												
2[h]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Laryngo-tracheomalacia												
Changes in respiratory parameters: (respiratory gases: supportive care vs. NIV)												
3[i]	observational studies	serious	not serious	not serious	not serious	none	24	24			⨁⨁◯◯ LOW	Important
Discontinuation of NIV:												
2[j]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Benefit of NIV - improvement in growth parameter(s):												
1[k]	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Benefit of NIV - improvement in underlying condition(s):												
1[l]	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important

Adherence:												
1[m]	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Spinal muscular atrophy type 1												
Mortality: (NIV vs. supportive care)												
3[n]	observational studies	serious	not serious	not serious	not serious	none	24/111 (21.6%)	138/146 (94.5%)	**RR 0.37** (0.25 to 0.54) z=5.16 p<0.0001	**595 fewer per 1000** (from 435 fewer to 709 fewer)	⨁⨁◯◯ LOW	Very important
6[o]	observational studies	serious	not serious	not serious	not serious	none					⨁⨁◯◯ LOW	Very important
Hospitalization: (per patient/per year)												
3[p]	observational studies	serious	not serious	not serious	not serious	none	n/a	n/a			⨁⨁◯◯ LOW	Very important
3[q]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Benefit of NIV - improvement in growth parameter(s):												
3[r]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁⨁◯◯ LOW	Important
Benefit of NIV – NIV facilitated extubation:												
3[s]	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Changes in respiratory parameters: (respiratory gases)												
1[t]	observational study	moderate	not serious	not serious	not serious	none	-	-			⨁⨁◯◯ LOW	Important
Central congenital hypoventilation syndrome												
Changes in respiratory parameters: (changes in respiratory gases post-NIV initiation)												
2[u]	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Discontinuation of NIV:												
2[v]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Benefit of NIV – improvement in growth parameter(s):												
2[w]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Mask complication(s):												
2[x]	observational studies	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important
Adherence:												
1	observational study	serious	not serious	not serious	not serious	none	-	-			⨁◯◯◯ VERY LOW	Important

CI: Confidence interval; n/a – data not available; NIV – non-invasive ventilation; **RR:** Risk ratio

a. Refer to Table 2.10 in Appendix I for risk of bias assessment of individual studies.
b. Two cohort studies (Downey 2000 and McNamara 1999), two case-control studies (Harrington 2003 and McNamara 1999), one control before-after (McNamara 1995).
c. Two cohort studies (Leonardis 2013 and Robison 2013), and one case series (Liu 2012); reported separately because no control group was present.
d. Three cohort studies (Downey 2000, McNamara 1999, Rosen 2010), one control before-after (McNamara 1995), and one case-control study (Guilleminault 1995).
e. One case series (Leboulanger 2010) and one cohort study (Amaddeo 2016).
f. One case series (Leboulanger 2010) and one cohort study (Amaddeo 2016).
g. Two cohort studies (Amaddeo 2016 and Kam 2015).
h. One case series (Leboulanger 2010) and one cohort study (Amaddeo 2016).
i. One bench study (Essouri 2005), one case-control study (Fauroux 2001), and one cohort study (Zwacka 1997).
j. One case-control study (Fauroux 2001) and one cohort study (Shatz 2004).
k. One case-control study (Fauroux 2001).
l. One cohort study (Shatz 2004).
m. One case-control study (Fauroux 2001).
n. Consist of two case series (Bach 2002 and Gregoretti 2012) and one cohort study (Bach 2007).
o. Consist of 4 cohort studies (Lemoine 2012, Otonello 2011, Chatwin 2011, and Vasconcelos 2005) and 2 case series (Bach 2000 and Birnkrant 1998); reported separately because they only reported results of NIV group as comparison group was not present.
p. Consist of two case series (Bach 2002 and Gregoretti 2012) and one cohort study (Bach 2007).
q. Consist of 2 cohort studies (Otonello 2011 and Lemoine 2012) and one case series (Bach 2000); reported separately because hospitalizations were compared to a supportive care group (Lemoine 2012) or there was no comparison group (Otonello 2011 and Bach 2000).
r. Two cohort studies (Bach 2007 and Ottonello 2011) and one case series (Bach 2002).
s. Two case series(Bach 2000 and Birnkrant 1998) and one cohort study (Ednick 2008).
t. One control before-after study (Petrone 2007).
u. Two case series (Tibballs 2003, Hartmann 1994).
v. One case series (Hartmann 1994) and one cross-sectional study (Ramesh 2008).
w. One case series (Hartmann 1994) and one content analysis (Noyes 1999).
x. One case series (Tibballs 2003) and one cross-sectional study (Ramesh 2008).
y. One case series (Hartmann 1994).

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CHAPTER 3: THE USE AND OUTCOMES OF LONG-TERM NON-INVASIVE VENTILATION IN INFANTS

3.1 ABSTRACT

Background: Non-invasive ventilation (NIV) is increasingly used to treat sleep and respiratory disorders in children; however, there are no treatment approaches specific for infants. The aim of this study is to compare NIV use between infants and older children to determine whether infants represent a distinct group within the pediatric NIV population, and may require separate treatment strategies.

Methods: This is a 10 year retrospective cohort study of all infants and children using long-term NIV. Infants were matched to older children in a 1:2 ratio based on sex and closest date of NIV initiation. Medical charts and sleep laboratory records were reviewed to extract demographic, clinical characteristic, and health outcome data.

Results: The most common underlying condition necessitating NIV in infants and older children was upper airway disorders; however, infants had more cardiopulmonary disease (16% vs 6%, p=0.002). Infants had more co-morbidities (98% vs 88%, p=0.003) and required more additional technology (36% vs 16%, p<0.001). CPAP was the most commonly used mode of NIV in both groups. Both infants and older children had similar improvements in sleep and respiratory parameters from a diagnostic to titration polysomnography. Clinic discharge rates from NIV clinic were similar for both groups; however, infants primarily ceased NIV due to improvements in underlying disease conditions (42% vs 30%, p=0.038), while older children transferred to other services (9% vs 35%, p<0.001).

Conclusions: Differences in primary underlying disease conditions, co-morbidities, NIV technology, and NIV outcomes support infants as a distinct group with respect to NIV therapy within the pediatric NIV population. These findings suggest a distinct approach to long-term NIV use in infants is warranted.

3.2 INTRODUCTION

The number of children requiring long-term respiratory support in the outpatient setting is increasing,[1-7] at least in part, due to improvements in the survival of children with complex medical illness[8-11]. Over the past two decades, there has been a shift from using long-term invasive mechanical ventilation (IMV) to non-invasive therapies.[12,13] The use of non-invasive ventilation (NIV), a method of delivering positive pressure breathing support via an interface outside the airway, has become the standard of care for providing long-term respiratory support for infants and older children with sleep and breathing disorders.[13,14] Reasons for the shift towards non-invasive therapies (such as continuous positive airway pressure (CPAP) and bi-level ventilation (BPAP)), include improvements in ventilator technology[8,12,14], avoidance of complications associated with IMV[9,15,16], and a growing recognition by clinicians and families of NIV as a viable alternative respiratory therapy.[8,12-14]

Although the use of NIV for all children with sleep and breathing disorders has been increasing, there is less data on the use and outcomes of NIV in infants.[17-19] The available data suggests that the current treatment approach to NIV therapy is similar in both infants and older children. However, there are key differences in the sleep and breathing physiology in infants when compared to older children[20,21] that may impact response to NIV. For example, both total sleep duration and the proportion of total sleep time spent in rapid eye movement (REM) sleep is higher in early life and decreases across infancy and childhood.[20-23] Arousals, defined as temporary changes in sleep stage or sleep stage, are common after birth and decrease across the first year of life.[21,24] The central control of breathing is immature at birth and matures in the following months, resulting in an increased variability with respect to ventilation in infants.[21,25] Respiratory events, including both central and obstructive events, commonly occur even in

otherwise healthy infants and decrease with age.[26,27] The increased time spent sleeping, higher proportion of time spent in REM sleep, and increased predisposition to respiratory events that occur during sleep demonstrate an increase in the risk for consequences of breathing problems, and potential differences in response to respiratory support in infants compared to older children.

To date, there are no studies comparing NIV therapy between infants and older children. Comparing the use and outcomes of NIV between these two groups will help us understand whether infants may require a separate treatment approach from older children. Therefore, the aim of our study is to compare the clinical characteristics, technology, and outcomes of infants and older children using long-term NIV to determine whether infants represent a distinct cohort in the pediatric NIV population. The results of our study will help clinicians determine whether similar or separate treatment strategies are required when starting infants and older children on long-term NIV therapy.

3.3 METHODS

3.3.1 Study design and participants

This is a 10-year retrospective cohort study with the comparing of long-term NIV use for infants and older children. It is part of a larger retrospective review of all children using long-term NIV in the province of Alberta from January 2005 through December 2014. Infants were defined as age $\leq$ 2 years and older children as age 2-18 years based on age guidelines used by the Public Health Agency of Canada.[28] Long-term NIV use was defined as use for a minimum of three months outside of an acute care setting. Infants were matched to older children in a 1:2 ratio based on sex and the closest date of NIV initiation to ensure contemporary comparisons.

3.3.2 Data Collection

Data were collected from the medical charts and sleep laboratory records of all children using long-term NIV at the Stollery Children's Hospital and Alberta Children's Hospital, Alberta. These two participating institutions are the only two publicly funded pediatric sleep labs in Alberta, and therefore represent the majority of, if not all, children using long-term NIV in Alberta. The Health Research Ethics Board for both institutions approved the study.

Data were collected at baseline and two follow-up times from medical charts and sleep study charts. Sleep studies could be diagnostic polysomnography (PSG) studies, split-night studies (including a diagnostic and titration component), or titration studies, and were performed using standard infant and child procedures. Data collection and scoring of PSGs were completed by an experienced technician following the guidelines of the American Academy of Sleep Medicine.[29]

Population characteristics that were collected from charts included age, sex, ethnicity, primary underlying disease category, co-morbidities (defined as any diagnosis aside from the primary underlying diagnosis), history of previous upper airway surgery, and baseline sleep and respiratory parameters. Data collected on NIV technology included location of NIV initiation, NIV type, NIV pressures, mask type, and use of any additional technology. Longitudinal outcome measures included physician reported improvements, and adherence rates from machine downloads (average hours of NIV used per night and % of days with NIV use for > 4 hours). Additional outcomes included number of infants discharging from clinic, , reasons for clinic discharge, and mortality outcomes. NIV clinic discharge reason was also identified and classified

as improvements in the underlying condition, NIV refusal (parents/children that declined continuing on NIV), or transfer of services (to adult services, another NIV provider, or out-of-province care) To compare changes in sleep and respiratory parameters over time, parameters were compared between a baseline diagnostic and titration PSG (full or split night studies) or between a baseline diagnostic and the first titration PSG after 3 months of NIV use. Data were entered and stored in an electronic REDCap research database.[30]

3.3.3 Analysis

Analysis was performed using IBM SPSS Statistics version 24.0 (SPSS, Inc., Chicago, IL). Summary statistics were reported as median (IQR) or frequencies (n, %) as appropriate. Chi-square test or Fisher's exact test were used to analyze categorical variables and Mann-Whitney U test was used to compare continuous variables between groups. Wilcoxon Signed Ranks test was used to compare sleep and respiratory parameters between paired diagnostic and titration PSG studies. Kruskall-Wallis test was used to compare median adherence between age groups <1 year, 1-2 years, and >2 year. Odds ratios with 95% CI or difference in medians with estimated Hodges-Lehman 95% CI were calculated to determine a measure of association for two dichotomous or continuous variables respectively. Logistic regression was used for multi-variable analysis of outcomes such as improvement of the underlying condition, NIV refusal, continuation of ventilation, and mortality. To determine variables for inclusion in multi-variable analysis, demographic, sleep and respiratory parameters, NIV technology, and adherence variables that had a $p<0.20$ on univariate analysis were tested in a logistic regression model. The 10-year study period was divided into three equal epochs to assess timing of NIV start in the regression model. Since our study is a comparison between infants and older children, age at

NIV initiation was included in all models. A p-value of <0.05 on analysis was considered to be statistically significant, and a post-hoc Bonferroni correction was applied for multiple comparisons. As an example, the logistic regression procedure for determining independent predictors of mortality is described in detail in Appendix II of this thesis.

3.4 RESULTS

Data were collected on 622 children, of which 122 (20%) were infants; 120 infants were matched to 240 older children for this study with insufficient appropriate matches for 2 infants. The median age of NIV initiation in infants and older children was 9.0 (12.0) months and 108.5 (91.8) months respectively (Table 3.1). Fifty-seven percent of infants and older children were male, and ethnicity was similar between both groups. The primary underlying disease category necessitating NIV differed between groups, with older children having more upper airway conditions and infants having more cardiopulmonary disease. Infants also had a higher number of underlying co-morbidities compared to older children.

Baseline sleep and respiratory parameters also differed between infants and older children (Table 3.1). Infants had a lower median total sleep time compared to older children. As expected, infants spent a higher proportion of total sleep time in REM sleep, and had a higher total apnea-hypopnea index (AHI), obstructive AHI, and central AHI compared to older children. Infants also spent a higher amount of total sleep time with oxygen saturations < 90%.

There were differences between both groups with respect to NIV technology use. Older children were more likely to start NIV in a home-based setting compared to infants (46% vs 84%,

p<0.001, Table 3.2). Infants were more likely to use a nasal interface, BPAP ventilation and require additional technology compared to older children. Recommended CPAP pressures were slightly higher in older children, but BPAP pressures were comparable between both groups at a baseline visit. Infants received more home-care support compared to older children (67% vs 26%, p<0.001).

Treatment response and outcomes after starting NIV therapy showed both similarities and differences between groups. Data for sleep and respiratory parameters from a diagnostic to titration PSG showed that older children had a greater decrease in their total sleep time post-NIV therapy compared to infants, and infants had a greater decrease in the total sleep time with oxygen saturations < 90% (Table 3.3). The change from diagnostic to titration PSG for all other sleep and respiratory parameters was similar between infants and older children. These included a significant decrease in the total and obstructive AHI from diagnostic to titration study in both groups (Figure 3.1). The average hours of NIV used per night was similar between groups for the first follow-up visit, but differed in the second visit, with infants using NIV for more hours than older children (Table 3.3). The percent of days with NIV use for >4 hours/24h was similar for infants and older children at both of the two follow-up visits. After splitting the infants into two <1 year and 1-2 years of age, the average hours of NIV use per night was similar between the <1 year, 1-2 year, and >2 year groups at both the follow-up visits (4.2 hrs vs 6.3 hrs vs 6.2 hrs, p=0.19) and (7.1 hrs vs 8.4 hrs vs 6.3 hrs, p=0.06) respectively. Likewise, the percent of days with NIV use >4 hours was also similar between the three groups at both follow-up visits (43% vs 81% vs 71%, p=0.20) and (80% vs 83% vs 67%, p=0.60) respectively.

While clinic discharge rates were similar between infants and older children, the reasons for discharge differed between both groups (Table 3.3). Infants predominantly discontinued because of improvements in the underlying condition or switch to IMV. By contrast, older children were primarily discharged from clinic because of transfer to other services.

Binomial logistic regression was performed to understand the strongest determinants of outcomes including clinic discharge due to improvements in the underlying condition, clinic discharge because of NIV refusal, continuation of NIV ventilation, and mortality. There were no significant independent predictors of improvement in the underlying condition and NIV refusal. Increasing age and a higher adherence rate (% of days with NIV use >4 hrs during the second follow-up visit) were the strongest predictors of continuing on NIV (Table 3.4). The requirement of additional technology was the only predictor of mortality.

3.5 DISCUSSION

To our knowledge, this is the first study comparing the use, technology, and outcomes of long-term NIV for infants and older children. Infants had more co-morbidities and required more additional technology than older children, potentially making them a more complex group. Despite similar incidence of central nervous system disease and neuromuscular disease, the use of BPAP was more common in the infant population. Changes in the majority of sleep and respiratory parameters were similar between both groups, highlighting the efficacy and viability of NIV as a method of providing long-term breathing support across childhood. Reasons for clinic discharge differed, demonstrating that infants may have a wider spectrum of outcomes, including improvement or switch to invasive ventilation, whereas older children predominantly

continued on long-term NIV. Somewhat surprisingly, adherence to NIV was similar for both infants and older children.

Differences in underlying clinical characteristics and technology use between infants and older children support the idea that infants represent a more medically complex group and may require separate treatment approaches. Medically complex children have been defined as those having multisystem disease, functional impairment of daily living, complex medical regiments, and/or technology dependence.[10,31] While our full cohort could be considered medically complex children because of the need for long-term NIV, our results have shown that infants have a significantly higher number of co-morbidities and require more additional technology than older children. Reasons for increased medical complexity in infants may include improvements in the survival of infants born premature and those with congenital conditions.[10,32] The treatment strategies for medically complex children are not well understood, especially in infancy.[10,31,32] However, the use of a clinical multidisciplinary approach to treat infants with multiple co-morbidities and technology use may help streamline medical care and improve adherence and outcomes for infants requiring long-term NIV.

Although the most common type of NIV used in both groups was CPAP, more infants were using BPAP compared to older children. CPAP is used in conditions where upper airway obstruction is present, while BPAP is beneficial for disorders resulting in abnormal central ventilatory drive or resulting in muscle weakness, as it can help unload respiratory muscles and improve alveolar ventilation.[6,33,34] Since upper airway disorders occurred most frequently for both groups in our population, the higher rates of CPAP use in both groups seems appropriate.

With the incidence of CNS and NMD being similar for both infants and older children, it is interesting that the rates of BPAP use were significantly higher in infants. Lack of infant-specific guidelines around the use of long-term NIV may be a factor for clinicians deciding whether to initiate an infant on CPAP or BPAP. More infants start NIV in an acute care setting without a prior PSG, and, therefore, may be initiated and subsequently continued on BPAP therapy after being transferred home. Additionally, BPAP is funded by the provincial health system in Alberta while CPAP is not, which may be another factor influencing clinicians when deciding between the two technologies. Infant-specific guidelines around the use of long-term NIV would provide a standard for decision making, and the pattern of technology used described here support a need to re-evaluate government funding protocols.

Improvements in sleep and respiratory parameters post-NIV initiation emphasize the importance of NIV therapy for normalizing sleep and breathing parameters in both infants and older children. Complications of disrupted sleep and breathing have been linked to abnormal growth, failure to thrive, and cognitive impairment in infants[35,36], and cardiovascular[37-39], metabolic[40,41], and adverse neurobehavioural[42,43] outcomes in older children. Our analyses demonstrated improvements in sleep and respiratory parameters after starting NIV therapy, such as a higher % of REM sleep, decrease in the total and obstructive AHI, and less TST with oxygen saturations below 90%. These results are similar to those reported in other infant studies reporting on improvement in PSG parameter with NIV for infants with upper airway disorders.[1,2,5,19,33,44-50] The results further highlight that NIV is a viable and alternative method of providing long-term respiratory support in infants with disorders of sleep and breathing. Future research should

include studies on infants sub-grouped by disease categories to help determine the impact of clinical characteristics on sleep and respiratory parameters.

Contrary to expectations, adherence to NIV therapy was similar between infants and older children. Previous studies have established that adherence is a common problem with children using NIV therapy[51-53]; however, there are few studies focusing on challenges to NIV adherence in infants.[54] Removal of NIV masks during sleep has remained a problem in the older child population; however, this problem is likely minimal in most infants as they lack the manual dexterity remove the NIV mask. This should, theoretically, improve the total time infants are using NIV, and therefore adherence. The comparable adherence in our infant and older child groups suggests that parents/caregivers may be removing the mask in infants, which can impact adherence in the infant population. It is important moving forward to work with parents/caregivers and children to understand barriers to adherence to help improve outcomes in both the infant and older child population.

There were several limitations to our study. As this was a retrospective chart review, information collected from the medical notes in the charts may have been missing. Not all infants and children had follow-up clinic visits or sleep studies; infants and children who started on NIV near the end of our data collection period had a shorter length of follow-up. However, missing clinical and PSG data were similar between infants and older children and therefore, are unlikely to explain differences identified between infants and older children. In addition, infants were defined as age 0-2 years based on a previously established definition. This cut-off is not

reflective of an important physiological marker, therefore, may not represent the ideal cut-point to define important changes for long-term NIV use.

3.6 CONCLUSIONS

Our results highlight that infants represent a distinct group within the overall pediatric NIV population in Alberta. Infants differed from older children with respect to the underlying disease category necessitating NIV. Infants had more co-morbidities, required more additional technology, and used more BPAP than older children. Improvements in sleep and respiratory parameters, such as % REM sleep, and total and obstructive AHI were similar for both groups. While infants primarily discharged from NIV clinic because of improvements in underlying conditions, older children were mostly transferred to other services. Based on differences in underlying population characteristics, NIV technology, and outcomes on NIV therapy, it is reasonable to conclude that infants represent a distinct group within the overall pediatric NIV cohort. These differences highlight the need for infant-specific treatment strategies and guidelines around the use of long-term NIV.

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Table 3.1: Comparison of baseline clinical characteristics including respiratory parameters for infants and older children using long-term non-invasive ventilation.

Characteristics	Infants (n=120)	Older children (n=240)	Odds ratio (95% CI) or difference in median (estimated 95% CI)
Age (months), median (IQR)	9.0 (12.0)	108.5 (91.8)	
Males, n (%)	68 (57)	136 (57)	
Underlying disease category, n (%)			
Upper Airway	55 (47)	144 (61)	0.56 (0.36 to 0.87) *
Central Nervous System	26 (22)	38 (16)	1.47 (0.84 to 2.57)
Neuromuscular	18 (15)	40 (17)	0.88 (0.48 to 1.62)
Cardiopulmonary	19 (16)	14 (6)	3.04 (1.47 to 6.31) **
Co-morbidities, n (%)	117 (98)	212 (88)	5.15 (1.53 to 17.31)†
Co-morbidity distribution, n (%)			
0 co-morbidities	3 (3)	28 (12)	0.19 (0.06 to 0.65) **
1-2 co-morbidities	46 (38)	117 (49)	0.65 (0.42 to 1.02)
3-4 co-morbidities	35 (29)	62 (26)	1.18 (0.73 to 1.93)
5+ co-morbidities	36 (30)	33 (14)	2.69 (1.57 to 4.60) †
Prior adenoidectomy and/or tonsillectomy, n (%)	31 (27)	125 (54)	0.31 (1.19 to 0.51) †
Baseline diagnostic PSG data, median (IQR)			
TST (min)	234 (168)	308 (222)	74 (19.70 to 87.10) **
Sleep efficiency (%)	83 (14)	86 (14)	3 (-0.40 to 4.40)
REM sleep (% of TST)	23 (17)	15 (10)	-8 (-11.10 to -5.80) †
Arousal index (events/hr)	10 (10)	8 (10)	-2 (-1.80 to 2.20)
Total AHI (events/hr)	23 (28)	10 (17)	-13 (-13.20 to -5.00)†
Obstructive AHI (events/hr)	16 (27)	8 (14)	-8 (-9.20 to -3.00) †
Central AHI (events/hr)	2 (6)	1 (3)	-1 (-1.20 to 0.00) *
% TST with SpO_2 < 90%	4 (18)	0.3 (5)	-3.7 (-4.00 to -0.70) †
% TST with $TcCO_2$ > 50mmHg	1 (36)	0.0 (18)	-1(-1.00 to 0.00)

AHI – apnea-hypopnea index; Auto-PAP – automatic positive airway pressure; BPAP – bi-level positive airway pressure; CI – confidence interval; CPAP – continuous positive airway pressure; IQR – interquartile range; OR – odds ratio; PSG – polysomnography; SpO_2 – arterial oxygen saturation; $TcCO_2$ – transcutaneous carbon dioxide saturation; A/T – adenoidectomy and/or tonsillectomy; TST – total sleep time

*p<0.05, **p<0.01, †p<0.001

Table 3.2: Comparison of NIV technology use for infants and older children using long-term non-invasive ventilation.

NIV technology	Infants (n=120)	Older children (n=240)	Odds ratio (95% CI) or difference in median (estimated 95% CI)
Location to start NIV, n (%)			
Home (pre-titration)	20 (17)	64 (27)	0.55 (0.32 to 0.97) *
Home (post-titration)	45 (38)	137 (57)	0.45 (0.29 to 0.71) **
Hospital ward	27 (23)	17 (7)	3.83 (1.99 to 7.37) †
NICU/PICU	27 (23)	21 (9)	3.05 (1.64 to 5.66) †
Interface type, n (%)			
Nasal	97 (95)	132 (61)	12.64 (4.94 to 32.32) †
Full face	5 (5)	86 (39)	0.08 (0.03 to 0.20) †
NIV type , n (%)			
CPAP or Auto-PAP	76 (65)	194 (81)	0.44 (0.27 to 0.72) **
BPAP	41 (35)	46 (19)	2.28 (1.38 to 3.74) **
NIV pressures (cmH_2O), median (IQR)			
CPAP or Auto-PAP	8 (2)	9 (3)	1.00 (1.00 to 2.00) *
BPAP (IPAP)	13 (5)	16 (4)	3.00 (0.00 to 4.00)
BPAP (EPAP)	6 (4)	6 (2)	0.00 (-1.00 to 2.00)
Additional technology, n (%)			
Gastrostomy tube	33 (28)	32 (13)	2.47 (1.43 to 4.26) **
Nasogastric tube	7 (6)	4 (2)	3.66 (1.05 to 12.74) *
Supplemental oxygen	6 (5)	1 (0.4)	12.58 (1.50 to 105.72) **
Oral appliance	0 (0)	2 (1)	1.50 (1.40 to 1.62)
Cough assist	0 (0)	1 (0.4)	1.50 (1.40 to 1.62)

Auto-PAP – automatic positive airway pressure; BPAP – bi-level positive airway pressure; CPAP – continuous positive airway pressure; EPAP – expiratory positive airway pressure; IPAP – inspiratory positive airway pressure; NICU – neonatal intensive care unit; PICU – pediatric intensive care unit

*$p<0.05$, **$p<0.01$, †$p<0.001$

Table 3.3: Comparison of treatment response and outcomes for infants and older children using long-term non-invasive ventilation.

Treatment response and outcomes	Infants (n=120)	Older children (n=240)	Odds ratio (95% CI)
PSG indices[‡], median of differences (IQR)	Change from Dx PSG to Tx PSG	Change from Dx PSG to Tx PSG	
Total sleep time (TST) (min)*	-18 (200)	-62 (242)	
Sleep efficiency (%)	-1 (22)	-1.5 (21)	
REM sleep (%)	4 (18)	5 (19)	
Arousal index (events/hr)	-0.5 (6)	-2 (8)	
Total AHI (events/hr)	-6 (21)	-3 (12)	
Obstructive AHI (events/hr)	-5 (19)	-3 (11)	
Central AHI (events/hr)	0.0 (4)	0.0 (2)	
% TST with SpO_2 < 90%**	-2 (11)	-0.1 (3)	
% TST with $TcCO_2$ > 50mmHg	0.0 (12)	0.0 (7)	
Adherence (average hours used/night)			
First follow-up visit, median (IQR)	6.0 (7.2)	6.2 (5.1)	0.36 (-0.83 to 1.56)
Second follow-up visit, median (IQR)	8.1 (8.2)	6.3 (5.7)	-2.21 (-3.62 to 0.80)*
Adherence (% days with NIV use > 4hrs)			
First follow-up visit, median (IQR)	59 (70)	71 (64)	4.60 (-16.78 to 7.07)
Second follow-up visit, median (IQR)	83 (73)	67 (65)	-5.91(-6.76 to 18.59)
Physician reported improvements:			
6 to 12 month visit, (n,%)			
Sleep quality/daytime sleepiness	37 (42)	123 (62)	0.44 (0.26 to 0.73) **
Breathing during sleep	32 (36)	72 (36)	0.99 (0.59 to 1.67)
Mood/behavior	12 (14)	53 (27)	0.43 (0.22 to 0.85) *
School/learning/attention	10 (11)	47 (24)	0.41 (0.20 to 0.85) *
Overall general health	39 (44)	90 (45)	0.95 (0.57 to 1.56)
Discharged from clinic, (n,%)	73 (62)	120 (52)	1.51 (0.96 to 2.38)
Reasons for clinic discharge, (n,%)			
Improvement of underlying condition	25 (42)	27 (30)	2.04 (1.04 to 4.03) *
Patient/family decline	18 (31)	31 (30)	1.01 (0.50 to 2.02)
Physician recommendation	5 (9)	3 (3)	3.06 (0.70 to 13.28)
Transfer of services[†]	5 (9)	36 (35)	0.17 (0.06 to 0.46)
Switch to invasive ventilation	6 (10)	1 (1)	11.43 (1.34 to 97.47)*
Mortality, (n,%)	14 (19)	11 (9)	2.351 (1.00 to 5.50)

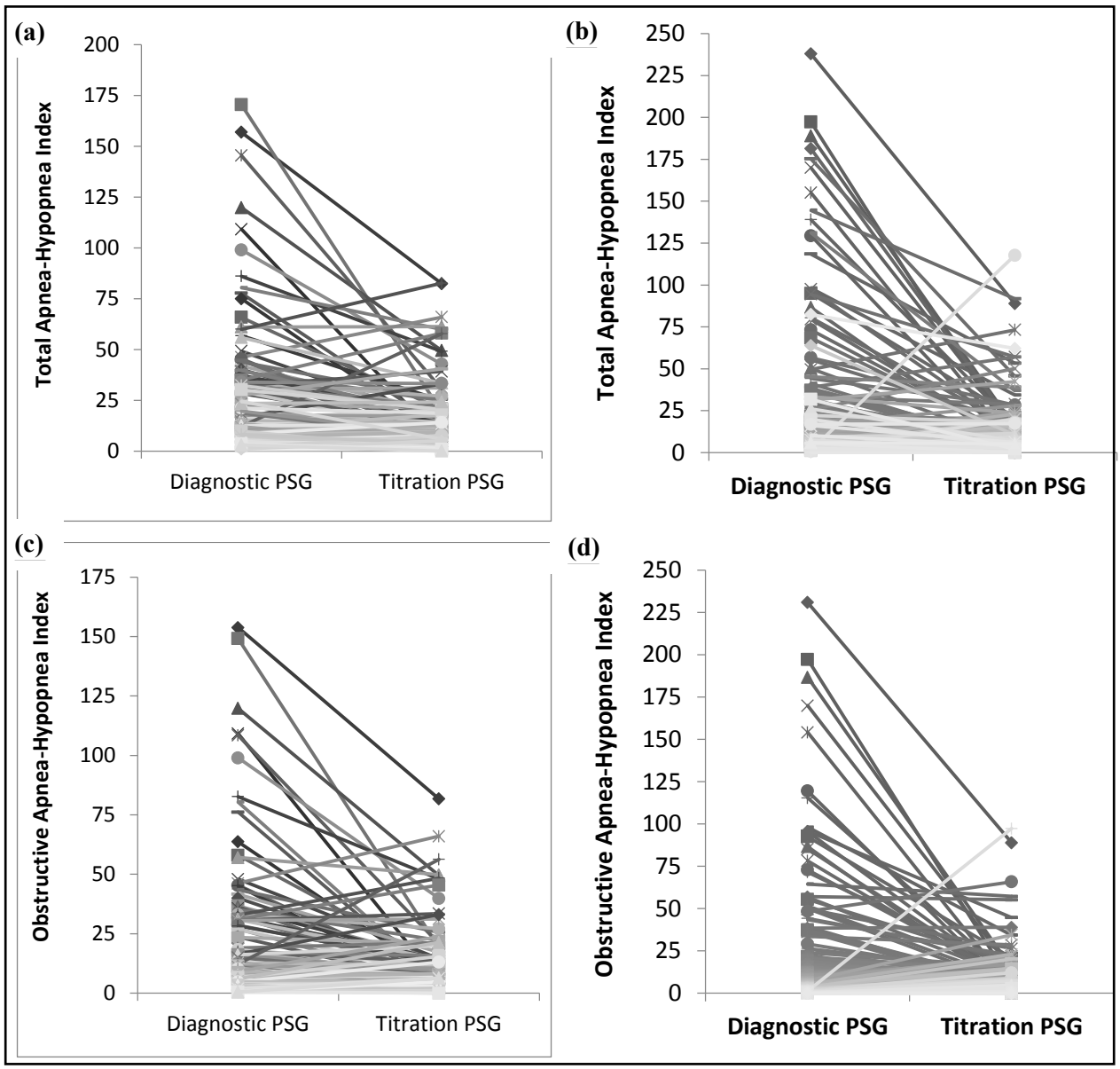
AHI – apnea-hypopnea index; Dx – diagnostic; NIV – non-invasive ventilation; PSG – polysomnography; REM – rapid eye movement; SpO_2 – arterial oxygen saturation; $TcCO_2$ – transcutaneous carbon dioxide saturation; TST – total sleep time; Tx – titration

*p<0.05; **p<0.01; [†]p<0.001

Table 3.4: Results of binomial logistic regression with reasons for clinic discharge as outcome variables and population characteristics and technology use as predictors.

Improvement of the underlying condition				
	B ± SE	p Value	Exp(B)	95% C.I. for Exp(B)
Constant	-1.940 ± 0.733	0.008	0.144	
NIV refusal				
	B ± SE	p Value	Exp(B)	95% C.I. for Exp(B)
Constant	2.278 ± 2.05	0.997	8.952	
Continuation of NIV				
	B ± SE	p Value	Exp(B)	95% C.I. for Exp(B)
Age (months)	0.008 ± 0.004	0.045	1.008	1.000 to 1.016
Adherence*	0.020 ± 0.007	0.004	1.021	1.007 to 1.035
Constant	-0.420 ± 0.562	0.455	0.657	
Mortality				
	B ± SE	p Value	Exp(B)	95% C.I. for Exp(B)
Additional technology	3.254 ± 1.201	0.007	25.905	2.460 to 272.849
Constant	-4.546 ± 1.688	0.007	0.011	

*% of days with NIV use >4hrs – second follow-up visit



PSG - polysomnography

Figure 3.1: Change from a diagnostic to titration PSG in (a) the total apnea-hypopnea index (AHI) in infants; (b) the total AHI in older children; (c) the obstructive AHI in infants; (d) the obstructive AHI in older children. There was a similar decrease in total AHI ($p=0.23$) and obstructive AHI ($p=0.36$) from a diagnostic to titration PSG for both infants and older children.

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CHAPTER 4: SUMMARY AND CONCLUSIONS

The results of this thesis show that infants can effectively use long-term non-invasive ventilation (NIV) and likely represent a distinct group within the overall pediatric population using NIV. The systematic review demonstrated NIV as an effective method of providing respiratory support for infants. The 10-year retrospective review showed differences in baseline clinical characteristics, baseline respiratory parameters, technology use, and outcomes of infants and older children using long-term NIV, which support the conclusion that infants represent a distinct cohort compared to older children. The results and conclusions of both studies highlight the need for continuing research on the topic of long-term NIV use in infants.

4.1. Aim 1: To perform a comprehensive review of the evidence currently available around the use of long-term non-invasive ventilation in the infant population.

The systematic review demonstrated that NIV is used to provide respiratory support in a range of infants. Infants with upper airway disorders, such as laryngomalacia, Pierre Robin sequence, or OSA secondary to multiple disorders, showed clinical improvements in respiratory parameters on sleep studies after NIV initiation. Studies on infants with neuromuscular disorders (NMD), which were almost exclusively limited to infants with spinal muscular atrophy type 1, showed a decrease in the number of hospitalizations, duration of hospitalization, and prolonged survival post-NIV therapy. Clinical outcomes in infants with central hypoventilation syndrome were limited, but also showed improvements in respiratory parameters post-NIV therapy. The weaker study design for the majority of studies analyzed in this systematic review limited the strength of the conclusions.

Overall, NIV appears to be an effective method of providing breathing support in infants with upper airway disorders, spinal muscular atrophy type 1, and central hypoventilation syndrome. The use of NIV in conditions similar to those that have shown benefit and improvements may be appropriate prior to invasive mechanical ventilation for certain groups. Prospective studies with stronger methodological design and the collection of NIV data in national disease databases can be beneficial moving forward towards increasing the understanding of NIV outcomes in infants using this therapy.

4.2. Aims 2, 3, and 4: To compare the clinical characteristics, technology use, and outcomes of long-term non-invasive ventilation for infants and older children.

The 10 year retrospective chart review demonstrated both similarities and differences with respect to NIV therapy in infants and older children. Improvements in sleep and respiratory parameters were similar between infants and older children, further supporting that NIV is a viable option for providing long-term respiratory support in a broad range of children. Similarities in adherence between both groups likely mean that parents/caregivers are removing the masks from infants, as the majority of infants do not have the manual dexterity to do so. Differences in underlying disease conditions, co-morbidities, baseline respiratory parameters, type of NIV used, additional technology use, and NIV outcomes support the conclusion that infants represent a distinct group within the overall pediatric NIV population.

This study highlights the need for infants to be studied distinctly within the overall population using long-term NIV, in order to fully understand the benefits and implications of NIV in infants.

4.3. Limitations

There were several limitations for the retrospective chart review comparing NIV use between infants and older children. Being retrospective in nature, it is already of a weaker study design as there are many possible areas of bias, including in the selection of participants, data collection, data analysis, measurement bias, and confounding bias. Methods to decrease bias were used, whenever possible, throughout the study.

4.3.1. Selection of participants

An overall research objective was established prior to study initiation. The establishment of proper inclusion and exclusion criteria was also done a priori to decrease selection bias.

4.3.2. Data collection

An electronic database with standardized data collection forms was created so that data was entered systematically. Variables within the data collection form were defined a priori and data collectors were educated about the electronic database, the forms, and the variables before data collection was initiated. Data collection was limited to 2-3 individuals, to decrease the incidence of collection bias. Variables were predominantly limited to check boxes to decrease the variability of data entry.

4.3.3. Data analysis

Data cleaning was performed to identify any outliers and incorrect data entry. To account for missing data, variables were only included in the study if < 25% of data was missing. In addition, if data for a variable was missing, the type and amount of missing data had to be

comparable between both groups for the variable to be included. A statistician was consulted after analyzing the data to confirm that the appropriate statistics were performed.

4.3.4. Measurement bias

Potential sources of measurement bias were also present in the retrospective chart review. Physician reported improvements were established based on information from chart notes and medical letters. As there were no standardized measurement of improvement, the data collected was may reflect any improvements noted during the clinic visit, increasing bias due to positive reporting of data. To balance for potential positive reporting, if there was no information for a physician reported improvement in the chart notes or letters, improvements were reported as 'no improvement'.

4.3.5. Confounding bias

There was an increased likelihood of confounding bias due to the retrospective design of the chart review. Seeing as all information was collected from charts, there was a high likelihood for missing data, thereby making it unfeasible to control all factors that may influence any particular outcome. Different methods to account for potential confounders were performed to help decrease confounding bias. Infants were matched to older children in a 1:2 ratio based on sex and closest date of NIV initiation, in order to decrease variability due to physiological differences and changes in NIV therapy over time. In addition, potential confounding variables were included in a logistic regression model to help understand the impact different covariates had on outcomes such as improvement in the underlying condition, NIV refusal, continuation of NIV, and mortality.

4.4. **Future directions**

Most studies in the systematic review had a retrospective, observational design, as did our 10-year chart review comparing infants and older children using long-term NIV. Retrospective studies are beneficial in that they are cost-effective, require less time, and can provide data for a large sample size. Drawbacks to retrospective studies include missing data and lack of outcome homogeneity. To overcome these challenges, the creation of online prospective clinic registries with systematic data collection tools would be beneficial. Data should be collected at standard time points for all children coming through the NIV clinic that meet pre-established inclusion criteria. Standardized outcome measures relevant to clinical care would provide clinician with improvement outcomes measures for clinical practice, in addition to enable improved analysis of the benefits of long-term NIV across clinical cohorts.

The observational nature of the majority of studies examining infants using NIV was also a limitation of study design, and highlighted the need for studies with stronger methodology such as clinical trials. The results of the systematic review, however, support that NIV appears to be an effective method of providing long-term respiratory support. Therefore, it would be unethical to perform a clinical trial where infants are randomized to treatment and no treatment arms. The development of within-subject clinical trials is an option to help address this limitation. N of 1 trials examining the impact of treatment in individual patients with before and after comparisons, and summation of individual subject results to establish group effects would be beneficial.[1] For example, standardized baseline clinical and respiratory variables could be measured with a

questionnaire and polysomnography for an infant in whom it appears respiratory therapy may be required. Afterwards, if the infant requires NIV, standardized outcome measures can be collected post-NIV initiation and before and after comparisons can be made to determine the effect of NIV therapy. The data collected on multiple infants can then be aggregated to determine the effect of long-term NIV for the entire cohort. This approach, with standardize baseline and follow-up measures at pre-determined time points, would improve on the methodological limitations of prior work.

While our 10-year review was multi-centred, previously published studies were primarily single-centred. The creation of an online data registry has the benefit of being accessible to multiple centres, allowing for collection of data from diverse populations and contributing to the generalizability of the findings. A primary research institute could be responsible for the analysis of the data, with contributions to data collection from multiple participating centres. Setting up a data registry that has relevance to clinical care by, for example, using outcomes measures with relevance to clinical practice, and providing this information for upload into patient electronic medical records, would provide benefit to the clinical team providing the respiratory support.

Current data on infants using long-term NIV is specific to certain disease conditions, including upper airway disorders, spinal muscular atrophy type 1, and congenital central hypoventilation syndrome. These are some of the most common conditions necessitating NIV in the infant population, which is why they have been predominantly studied. The results and outcomes obtained for these conditions, however, may not be applicable to other less commonly studied

conditions. The creation of an online, multi-centred data registry collecting data on all children coming through the NIV clinic can help to aggregate data on less common conditions.

Differences in the underlying clinical characteristics, technology use, and outcomes on NIV therapy support that infants represent a distinct group compared to older children. The higher number of infants using BPAP therapy may be, in part, due to CPAP not being provincially funded. Different funding models which can impact decision making about the type of NIV modality being established. Re-evaluation of government funding protocols may be beneficial to ensure that infants are being placed on the post appropriate NIV technology. In addition, there are currently no guidelines around the use of long-term home NIV in the pediatric population. The American Thoracic Society has recently released clinical practice guidelines for the management of children receiving invasive mechanical ventilation at home. With an increasing shift from invasive to non-invasive ventilation, the creation of clinical practice guidelines for infants using long-term home NIV will help to standardize care, and support examining how aspects of clinical care impact health and well-being outcomes for infants using NIV and their families.

4.5. Overall conclusions

The use of NIV appears to be an effective and viable method of providing long-term respiratory support in the infant population, and may help decrease the need for, and complications associated with, invasive ventilation. The creation of a data registry with standardized data collection for children using long-term NIV can help develop future multi-centred studies with

stronger methodology for infants using this therapy. Differences in the baseline clinical characteristics, technology use and outcomes of NIV between infants and older children support the idea that infants represent a distinct group within the overall pediatric population using NIV. The re-assessment of government funding protocols to include funding for CPAP would help ensure that the correct NIV therapy is being given based on underlying disease conditions. Furthermore, the development of clinical guidelines around the use of NIV in the infant population can help provide specialized care for this group by providing standards for decision making.

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APPENDIX I

Supplemental Table 2.8: Search strategy used in the Ovid Medline database for the scoping review to identify literature on the use of long-term non-invasive ventilation in children. The search strategy also included infant keywords to help identify studies on infants.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations & Ovid Medline(R): 1946 to November Week 1 2014
Original Search Date: 17 November 2014
Update Search Date: 29 April 2016

1. Continuous Positive Airway Pressure/
2. Noninvasive Ventilation/
3. Intermittent Positive-Pressure Breathing/
4. Ventilators, Negative-Pressure/
5. AVAPS.tw.
6. ((auto* or adaptive) adj2 (servoventilation or ventilation)).tw.
7. AutoSet*.tw.
8. ((bi level or bilevel) adj2 (airway* or air way* or assist* or breath* or positive pressure* or respirat* or ventilat* or support* or therap*)).tw.
9. BIPAP*.tw.
10. BPAP*.tw.
11. c flex.tw.
12. CNEP.tw.
13. (continuous negative adj2 pressure).tw.
14. (continuous positive airway* or continuous positive air way*).tw.
15. (continuous positive adj2 pressure).tw.
16. CPAP*.tw.
17. ((domicil* or home*) adj5 ventilat*).tw.
18. intermittent positive pressure breathing.tw.
19. IPPB*.tw.
20. ((long term or longterm) adj5 ventilat*).tw.
21. ((nasal* or mask*) adj2 (positive adj2 pressure)).tw.
22. ((nasal* or mask*) adj2 ventilat*).tw.
23. nCPAP*.tw.
24. ((negative pressure) adj2 (respirat* or ventilat*)).tw.
25. ((night* or nocturnal* or sleep*) adj5 ventilat*).tw.
26. NIPPV*.tw.
27. ((noninvasive adj5 ventilat*) or (non invasive adj5 ventilat*)).tw.
28. (noninvasive respiratory support* or non invasive respiratory support*).tw.
29. NPPV*.tw.
30. (positive pressure adj2 respirat*).tw.
31. REMstar*.tw.
32. (tank adj (respirat* or ventilat*)).tw.
33. VPAP*.tw.
34. or/1-33
35. Hypoventilation/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
36. Interactive Ventilatory Support/
37. Intermittent Positive-Pressure Ventilation/
38. Positive-Pressure Respiration/
39. Respiration, Artificial/
41. exp Sleep Apnea Syndromes/ pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
42. Ventilators, Mechanical/
43. ((airway* or air way* or breath* or inspirat* or respirat* or ventilat*) and (positive adj2 pressure)).tw.
44. intermittent positive pressure.tw.
45. IPPV*.tw.
46. (mechanical adj (respirat* or ventilat*)).tw.
47. (positive adj2 pressure adj (assist* or support* or therap*)).tw.
48. positive airway pressure.tw.
49. pulmonary ventilator*.tw.
50. respiratory support*.tw.
51. or/35-50
52. (noninvasive or non invasive or spontaneous*).mp.
53. 51 and 52
54. 34 or 53
55. exp Adolescent/
56. exp Child/
57. exp Infant/
58. exp Minors/
59. exp Pediatrics/
60. exp Puberty/
61. exp Schools/
62. adoles*.mp.
63. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).mp.
64. (boy* or girl* or teen*).mp.
65. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).mp.
66. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).mp.
67. minors*.mp.
68. (paediatric* or peadiatric* or pediatric*).mp.
69. (prepubescen* or pubescen* or pubert*).mp.
70. or/55-69
71. 54 and 70
72. (case reports or comment or editorial or letter).pt.
73. 71 not 72
74. exp animals/ not humans.sh.
75. 73 not 74
76. limit 75 to yr="1990 -Current"
77. remove duplicates from 76

40. Respiratory Insufficiency/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]

Supplemental Table 2.9: Characteristics and outcomes of studies included in the systematic review on infants using long-term non-invasive ventilation (NIV). Studies without any reported infant NIV outcomes have been listed first. Studies have been classified according to the primary underlying disease category reported. Studies with multiple primary disease categories have been included at the end of the table.

First Author, Year	Study design	Study duration	Total n (males)	Infants on NIV	Age (mean±SD or median (range) unless otherwise stated)	Interventions	Infant NIV outcomes
Articles with no NIV outcomes							
Afsharpaiman[1] 2011	Quantitative: Observational (cohort)	15 yr	n=46 (22)	n=7	Overall: 3.9 yr; Infants: < 2 yr (n=7)	CPAP (n= 9) AT (n=13)	None (only reported the number of subjects on NIV)
Barnerias[2] 2014	Quantitative: Observational (cross-sectional)	20 yr	n=222 (n/a)	n=8	Overall: 3 mo (0.5 – 8 mo)	NIV (n=8)	
Chatwin[3] 2015	Quantitative: Observational (cohort)	18 yr	n=449 (281)	n=59[b]	Overall: 10 yr (3-15 yr) Infants: < 1 yr (n=59)	CPAP (n=57) Bi-level (n=392)	
Cheng[4] 2011	Quantitative: Observational (case series)	5 yr	n=6 (n/a)	n=6	26 d - 11 mo	CPAP (n=6)	
Daniel[5] 2013	Quantitative: Observational (cross-sectional)	12 yr	n=39 (16)	n=18	n/a	CPAP (n=18)	
Ioos[6] 2004	Quantitative: Observational (cohort)	n/a	n=180 (n/a)	n/a	19±17mo	n/a	
Marcus[7] 1995	Quantitative: Observational (cross-sectional)	n/a	n=94 (60)	n=3[b]	Overall: < 1 – 19 yr < 1 yr (n=3)	CPAP (n=94)	
Massa[8] 2002	Quantitative: Observational (cohort)	5 yr	n=66 (39)	n=9[b]	Overall: 5.9±5.1 yr < 1 yr (n=18)	CPAP (n=66)	
Ramirez[9] 2012	Quantitative: Observational (case-series)	18 mo	n=97 (n/a)	n=18	Overall: Infants: < 2 yr (n=18)	CPAP and bi-level (n/a)	
Zhou[10] 2012	Quantitative: Observational (cohort)	2 yr	n=14 (12)	n=6[b]	Overall: 50 d – 12 yr Infants < 1 yr (n=6)	Bi-level (n=13) CPAP (n=1)	
Articles on upper airway disorders: Obstructive sleep apnea							

Downey[11] 2000	Quantitative: Observational (cohort)	7 yr	n=18 (n/a)	n=10[c]	Overall: < 2 yr	CPAP (n=14) IMV (n=4)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV
Guilleminault[12] 1995	Quantitative: Observational (cohort)	n/a	n=74 (35)	n=74	24±9 wk	CPAP (n=74)	▪ Number of subjects on NIV ▪ Discontinuation of NIV
Harrington[13] 2003	Quantitative: Observational (case-control)	n/a	n=18 (11)	n=6	13±4 wk	CPAP (n=6)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters
Leonardis[14] 2013	Quantitative: Observational (cross-sectional)	4 yr	n=126 (86)	n=18	NIV group: 16 mo	None (n=33) NIV (n=18) IMV (n=7)[g]	▪ Number of subjects on NIV ▪ Changes in respiratory parameters
Liu[15] 2012	Quantitative: Observational (case series)	n/a	n=3 (2)	n=2	Overall: 1 mo – 5 yr Infants: 1 mo – 7 mo	CPAP (n=2) Bi-level (n=2)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Benefit of NIV - growth parameters
McNamara[16] 1995	Quantitative: Control Before-After	0.5 yr	n=5 (2)	n=5	8 – 12 wk	CPAP (n=5)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV ▪ Survival/Mortality
McNamara[17] 1999	Quantitative: Observational (case-control)	n/a	n=24 (13)	n=8	CPAP group: 10.8±1.3 wk	CPAP (n=8)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters
McNamara[18] 1999	Quantitative: Observational (cohort)	n/a	n=24 (15)	n=24	1 – 51 wk	CPAP (n=24)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV
Robison[19] 2013	Quantitative: Observational (cross-sectional)	4 yr	n=295 (196)	n=18	CPAP/Bi-level group: 15.6 mo (3-29 mo)	None (n=76) NIV (n=18) T&A (n=116) IMV (n=6)[g]	▪ Number of subjects on NIV ▪ Changes in respiratory parameters
Rosen[20] 2010	Quantitative: Observational (case series)	5.5 yr	n=16 (n/a)	n=6	Overall: < 2 yr	CPAP (n=6)	▪ Number of subjects on NIV ▪ Discontinuation of NIV
Articles on upper airway disorders: Pierre Robin sequence							
Amaddeo[21] 2016	Quantitative: Observational (cohort)	1 yr	n=44 (n/a)	n=9	Infants: 0-2 mo	CPAP (n=9)	▪ Number of subjects on NIV ▪ Adherence to NIV ▪ Hospitalization (duration) ▪ Changes in respiratory parameters ▪ Discontinuation of NIV
Kam[22]	Quantitative:	11 yr	n=139	n=20[a]	23 mo (5d – 8 yr)	None (n=61)	▪ Number of subjects on NIV

2015	Observational (cohort)		(72)			CPAP (n=20) IMV (n=19)[g]	▪ Hospitalizations (duration)
Leboulanger[23] 2010	Quantitative: Observational (case series)	10 yr	n=7 (3)	n=7	1 – 10 mo	CPAP (n=5) Bi-level (n=2)	▪ Number of subjects on NIV ▪ Adherence to NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV
Articles on upper airway disorders: Laryngo-tracheomalacia							
Essouri[24] 2005	Quantitative: Control Before-After	n/a	n=10 (5)	n=10	9.5 mo (3-18 mo)	None (n=10) CPAP (n=10) Bi-level (n=10)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters
Fauroux[25] 2001	Quantitative: Control Before-After	n/a	n=12 (10)	n=5	Overall: 32.9±25.8 mo Infants: 8-19 mo	None (n=12) Bi-level (n=12)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Benefit of NIV - growth parameters ▪ Adherence to NIV ▪ Discontinuation of NIV
Shatz[26] 2004	Quantitative: Observational (cohort)	3 yr	n=50 (36)	n=50	6.5±3.5 mo (1 – 18 mo)	Bi-level (n=9) CPAP (n=5)	▪ Number of subjects on NIV ▪ Improvement in underlying disease ▪ Discontinuation of NIV
Zwacka[27] 1997	Quantitative: Observational (case series)	n/a	n=10 (5)	n=10	3 wk – 5 mo	CPAP (n=7)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Benefit of NIV - growth parameters
Articles on upper airway disorders: Breath holding spells							
Guilleminault[28] 2007	Quantitative: Observational (case-control)	2.5 yr	n=19 (11)	n=14	31±3 wk	CPAP (n=14)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ NIV success/failure
Articles on neuromuscular disease: Spinal muscular atrophy type 1							
Bach[29] 2000	Quantitative: Observational (case series)	n/a	n=11 (6)	n=8	3-28 mo	Bi-level (n=11)	▪ Number of subjects on NIV ▪ Survival/Mortality ▪ Benefit of NIV - growth parameters ▪ Benefit of NIV - extubation ▪ Hospitalization (duration)
Bach[30] 2002	Quantitative: Observational (cohort)	5 yr	n=56 (n/a)	n=33	Overall for patient groups: NIV: 11.2±5.7 mo IMV: 10.8±5.0 mo Supportive: 6.0±1.3 mo	NIV (n=33) IMV (n=16) None (n=7)	▪ Number of subjects on NIV ▪ Hospitalizations (per patient-years) ▪ Survival/Mortality
Bach[31] 2003	Quantitative: Observational (case series)	n/a	n=3 (2)	n=3	4-11 mo	NIV (n=3)	▪ Number of subjects on NIV ▪ Benefit of NIV - growth parameters
Bach[32]	Quantitative:	13	n=92	n/a	Therapy group:	None (n=18)	▪ Number of subjects on NIV

2007	Observational (cohort)		(n/a)		None: 6.6±4.1 mo Bi-level: 10.6±5.7 mo IMV: 14.8±15.2 mo	Bi-level (n=47) IMV (n=27)	▪ Hospitalizations (per patient-years) ▪ Survival/Mortality
Birnkrant[33] 1998	Quantitative: Observational (case series)	2 yr	n=4 (3)	n=3	4 – 9mo	Bi-level (n=4)	▪ Number of subjects on NIV ▪ Benefit of NIV - extubation ▪ Survival/Mortality
Chatwin[34] 2011	Quantitative: Observational (cohort)	19 yr	n=13 (8)	n=13	4-24 mo	Bi-level (n=13)	▪ Number of subjects on NIV ▪ Benefit of NIV - growth parameters ▪ Survival/Mortality
Ednick[35] 2008	Quantitative: Observational (cohort)	3.5 yr	n=7 (1)	n=7	8.3±3.7 mo	Bi-level (n=7)	▪ Number of subjects on NIV ▪ Benefit of NIV – extubation
Gregoretti[36] 2013	Quantitative: Observational (case series)	18 yr	n=194 (103)	n=31	NIV group: 12.6±14.4 mo (0-42 mo) IMV group: 6.9±4.3 mo	None (n=121) NIV (n=31) IMV (n=42)	▪ Number of subjects on NIV ▪ Hospitalizations (per patient-years) ▪ Survival/mortality
Lemoine[37] 2012	Quantitative: Observational (cohort)	7 yr	n=49 (31)	n=49	Groups: NIV: 136 d (34-196 d) Supportive care: 69d (38-145 d)	None (n=23) Bi-level (n=26)	▪ Number of subjects on NIV ▪ Hospitalizations (number of visits) ▪ Survival/Mortality
Ottonello[38] 2011	Quantitative: Observational (cohort)	4 yr	n=16 (n/a)	n/a	Overall: < 3 yr 10.4±6.2 mo	NIV (n=16)	▪ Number of subjects on NIV ▪ Hospitalizations (per patient-years) ▪ Benefit of NIV ▪ Survival/mortality
Petrone[39] 2007	Quantitative: Control Before-After	n/a	n=9 (7)	n=9[a]	7 mo (2-33 mo)	Bi-level (n=9)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters
Vasconcelos[40] 2005	Quantitative: Observational (cohort)	11	n=22 (16)	n=7[a]	Overall: 5.5 yr (6mo-26 yr) SMA Type 1 group: 13 mo (3mo – 3 yr)	None (n=5) Bi-level (n=17)	▪ Number of subjects on NIV ▪ Benefit of NIV - growth parameters ▪ Hospitalizations (number of visits) ▪ Survival/mortality
Articles on neuromuscular disease: Multiple (spinal muscular atrophy type 1 and congenital myopathy)							
Han[41] 2015	Quantitative: Observational (cohort)	13.4	n=57 (n/a)	n/a	Overall: 7.7 mo (2-158mo) Infants with: SMA Type1: 6.6 mo (2-26) CM: 7.8 mo (3-121)	NIV (n=8) IMV (n=46)	▪ Number of subjects on NIV ▪ NIV success/failure ▪ Survival/mortality
Articles on central nervous system disease: Congenital hypoventilation syndrome							
Hartmann[42] 1994	Quantitative: Observational (case series)	n/a	n=9 (3)	n=6	22d – 52 mo	VNEP (n=9)[e] CPAP (n=3)[f]	▪ Number of subjects on NIV ▪ NIV success/failure ▪ Quality of life

							▪ Benefit of NIV – growth parameters ▪ Discontinuation of NIV
Noyes[43] 1999	Qualitative: Content analysis	n/a	n=7 (3)	n=5	66 d – 59 mo	VNEP (n=5) CPAP (n=1)[f] IMV (n=2)	▪ Number of subjects on NIV ▪ Quality of life ▪ Benefit of NIV – growth parameters ▪ Discontinuation of NIV
Ramesh[44] 2008	Quantitative: Observational (cross-sectional)	n/a	n=15 (5)	n=7	Early start: 8 wk (5-26 wk) Late start: 8 yr (1.5-11 yr)	NIV (n=15)	▪ Number of subjects on NIV ▪ Benefit of NIV - extubation ▪ Mask complications
Tibballs[45] 2003	Quantitative: Observational (case series)	n/a	n=4 (2)	n=2	6 wk – 9 yr	Bi-level (n=4)	▪ Number of subjects on NIV ▪ Benefit of NIV – extubation ▪ Changes in respiratory parameters ▪ Mask complications
Articles on cardiorespiratory disease: Congenital heart disease							
Bunn[46] 2004	Quantitative: Observational (case series)	n/a	n=4 (0)	n=3	5-34 mo	NIV (n=4)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV
Articles on multiple underlying disease conditions							
Amaddeo[47] 2016	Quantitative: Observational (cohort)	1 yr	n=76 (39)	n/a	Overall for patient groups: Acute: 0.3 yr (0.1-13.5) Sub-acute: 0.6 yr (0.2-18.2) Chronic: 1.6 yr (0.1-19.5)	CPAP (n=64) Bi-level (n=12)	▪ Number of subjects on NIV ▪ Predictors of NIV requirement
Bertrand[48] 2006	Quantitative: Observational (cohort)	10.5 yr	n=35 (18)	n=9[a]	12 mo (5mo – 14 yr)	CPAP (n=1) Bi-level (n=8) IMV (n=26)	▪ Number of subjects on NIV ▪ Hospitalizations (per patient-years) ▪ Discontinuation of NIV ▪ Survival/Mortality
Fauroux[49] 2005	Quantitative: Observational (cross-sectional)	0.5 yr	n=40 (22)	n=16	Overall: 10.0 yr (0.6-18 yr) Infant: 1.8 yr (0.2-15.3 yr)[d]	NIV (n=40)	▪ Number of subjects on NIV ▪ Adherence to NIV ▪ Mask complications
Kherani[50] 2016	Quantitative: Observational (cohort)	23 yr	n=51 (30)	n=25	NIPPV: 0.6 yr (0.4-0.7 yr) IMV: 0.4 yr (0.1-0.7 yr)	NIV (n=25) IMV (n=26)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV ▪ Survival/Mortality
Markstrom[51] 2008	Quantitative: Observational (cohort)	7 yr	n=18 (11)	n=18	4 mo (1 – 12 mo)	Bi-level (n=18)	▪ Number of subjects on NIV ▪ Changes in respiratory parameters ▪ Discontinuation of NIV
Koontz[52] 2003	Quantitative: Observational (cohort)	n/a	n=20 (n/a)	n=6	1 – 2 yr	Bi-level (n=6)	▪ Number of subjects on NIV ▪ Adherence to NIV

AT- adenotonsillectomy; CPAP – continuous positive airway pressure; IMV – invasive mechanical ventilation; n/a – data not available/reported; NIV – non-invasive ventilation; SMA – spinal muscular atrophy

[a] Based on the mean/median age of the population during NIV initiation.
[b] Number of patients less than one year of age.
[c] 4 patients did not tolerate CPAP.
[d] Only includes infants in the obstructive sleep apnea group.
[e] VNEP failed in two patients.
[f] CPAP used in conjunction with VNEP.
[g] Full list of non-surgical and surgical interventions are in the full-text of article

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Supplemental Table 2.10: Assessment of risk of bias in studies included in the systematic review on long-term non-invasive ventilation in infants using the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool.[a]

First Author, Year	Confounding	Selection	Measurement of Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Results	Overall Risk of Bias (RoB) Assessment[b]
Obstructive sleep apnea							
Downey 2000	Moderate	Moderate	Serious	Serious	Serious	Serious	Serious
Guilleminault 1995	Serious	Serious	Serious	Serious	Serious	Moderate	Serious
Harrington 2003	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Leonardis 2013	Moderate	Serious	Moderate	Serious	Serious	Moderate	Serious
Liu 2012	Serious	Serious	Moderate	Moderate	Moderate	Serious	Serious
McNamara 1995	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Serious
McNamara 1999	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
McNamara 1999	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Robison 2013	Moderate	Moderate	Serious	Serious	Serious	Moderate	Serious
Rosen 2010	Moderate	Serious	Serious	Serious	Serious	Serious	Serious
Pierre Robin sequence							
Amaddeo 2016	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Kam 2015	Moderate	Moderate	Serious	Serious	Moderate	Moderate	Serious
Leboulanger 2010	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Laryngo-tracheomalacia							
Essouri 2005	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate
Fauroux 2001	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Serious
Shatz 2004	Moderate	Serious	Serious	Serious	Serious	Moderate	Serious
Zwacka 1997	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Spinal muscular atrophy type 1							
Bach 2000							
Bach 2002	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Bach 2007	Serious	Serious	Serious	Serious	Low	Moderate	Serious
Birnkrant 1998	Serious	Serious	Serious	Moderate	Serious	Serious	Serious
Chatwin 2011	Serious	Serious	Serious	Moderate	Moderate	Serious	Serious
Gregoretti 2013	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Lemoine 2012	Moderate	Serious	Serious	Moderate	Moderate	Moderate	Serious
Ottonello 2011	Moderate	Serious	Serious	Moderate	Moderate	Moderate	Serious

Vasconcelos 2005	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Congenital hypoventilation syndrome							
Hartmann 1994	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Noyes 1999	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Ramesh 2008	Moderate	Serious	Serious	Moderate	Serious	Serious	Serious
Tibballs 2003	Moderate	Serious	Serious	Moderate	Serious	Serious	Serious

[a]According to the Cochrane ROBINS-I tool: Sterne Jonathan AC, Hernán Miguel A, Reeves Barnaby C, Savović Jelena, Berkman Nancy D, Viswanathan Meera et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions BMJ 2016; 355 :i4919

[b] Criteria set out by the ROBINS-I tool:

- Low risk of bias – study is comparable to a well performed randomized trial within that domain;
- Moderate risk of bias – study is sound for a non-randomized study, but is not considered comparable to a well performed randomized trial within that domain;
- Serious risk of bias – study has some important problems within that domain;
- Critical risk of bias – the study is too problematic in this domain to provide any useful evidence on the effects of intervention;
- No information – no information on which to base a judgment about risk of bias within that domain.

Supplemental Table 2.11: Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement (Table 8)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, Table 2, online supplement Table 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Online supplement Table 10, 11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13, Tables 3-6, online supplement Table 9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13, Figure 2
Risk of bias across	22	Present results of any assessment of risk of bias across studies (see Item 15).	13,

studies			Table 7, Online supplement Table 10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: **www.prisma-statement.org**.

APPENDIX II

APPENDIX A: A step-wise procedure for performing a binomial logistic regression to determine the effect of baseline clinical characteristics, respiratory parameters, technology use, and adherence on mortality.

The results of the 10-year retrospective chart review on children using long-term non-invasive ventilation (NIV) showed that mortality was similar between infants and older children. However, it is unclear whether there are other factors contributing to the mortality outcome. To determine the independent predictors of mortality, a binomial logistic regression was performed. Logistic regression followed the methods described in the Laerd Statistics website (Laerd Statistics, 2017) and analysis was performed using IBM SPSS Statistics version 24.0 (SPSS, Inc., Chicago, IL).

Step 1: Determining if the assumptions have been met

In order to correctly perform a logistic regression, the following assumptions have to be met:

1. *The dependent variable must be a dichotomous variable.*
    - The dependent variable for this example is mortality (yes/no), which is dichotomous and satisfies the first assumption.

2. *One or more of the independent variables must be continuous or nominal.*
    - Variables such as age, number of co-morbidities, total apnea-hypopnea index (AHI), obstructive AHI, and central AHI, were continuous or nominal variables, satisfying the second assumption.

3. *There needs to be an independence of observations, and both the dependent variable and independent variables must be mutually exclusive and exhaustive.*

   - Our population was first divided into an infant or older child group, and then infants were matched to older children in a 1:2 ratio. Each child was only represented once in the final cohort, and all data with respect to dependent and independent variables was mutually exclusive to either the infant or older child group.

4. *A minimum of 15 cases are required per independent variable.*

   - The independent variable with the lower number of cases was ethnicity, which had n=216 cases, satisfying the above assumption.

5. *The continuous independent variables and the log transformation of the dependent variable must show a linear relationship.*

   - Testing for linearity was done using the Box-Tidwell procedure in SPSS, which tests for the linear relationship between continuous independent variables and the logit of the dependent variable. Based on this procedure, all of the continuous independent variables were found to be linearly related to the logit of each of the dependent variable, mortality.

6. *The independent variables cannot be highly correlated amongst themselves*

   - To test for multicollinearity, we tested the independent variables being included in the regression against each other using Chi-square tests for categorical variables and

Spearman correlation for continuous variables. The variables included in this analysis were not significantly correlated with each other.

Step 2: Determining which variables to include in the multivariable logistic regression

In order to determine which variables to include in the logistic regression, a purposeful selection of variables was performed. Underlying clinical characteristics, baseline respiratory parameters, NIV technology use, and adherence to NIV variables were analyzed by univariate analysis using a Chi-square test for categorical variables or a Mann-Whitney U test for continuous variables. Independent variables that had a $p<0.20$ on univariate analysis were included for multivariable analysis (Table 1). In addition, variables that have been identified as being clinically relevant to mortality, such as disease category, were also considered for inclusion in multivariable analysis (although in this instance, disease category had a $p<0.20$ and was included regardless). Age was included in the analysis as it was part of our hypothesis that there would be differences in outcomes between infants and older children. Variables such as total sleep time, percent of time spent in rapid eye movement (REM) sleep, and percent of total sleep time with oxygen saturations <90% were excluded from analysis, however, because of an underlying physiological association with the infant age group. History of upper airway surgery was excluded because of the strong association with older children.

Step 3: Creating models for multivariable logistic regression analysis

Once independent variables, or covariates, were chosen for inclusion, different models were created for multivariable analysis. Initially, a model with just a single covariate was created, and the significance of that covariate and the model was determined. Then covariates were added two

at a time to see whether there was still statistical significance or whether confounding occurred. Covariates that did not contribute to significance were removed from the model. This procedure was repeated multiple times with the step-wise addition of covariates and/or the removal of confounding covariates until a best-fit model was produced. This new model with then compared to the original model containing all the covariates, as well as the other models created in the step-wise process using the partial likelihood ratio test, to help choose the most appropriate model.

Step 4: Running the logistic regression model and interpreting the results

The best-fit model contained the variables ethnicity, disease category, number of co-morbidities, location of NIV initiation, and use of additional technology. These variables were entered into a logistic regression to determine their impact on mortality. The logistic regression model was statistically significant (Chi-square 39.75, $p<0.001$). It explained 46.1% (Nagelkerke R^2) of the variance in mortality, and was able to correctly classify 94.4% of cases. Of the five covariate that were included in the regression, only the use of additional technology was statistically significant (Table 2). According to the results of the regression, the use of additional technology increased was 25.9 times more likely to result in mortality. These results are likely because the use of additional technology is associated with children being more medically complex[2,3], and thus likely to have a more severe disease course and poorer outcomes. Similar methods were used to run logistic regression for other outcome variables.

Table 1: Variables included in a binary logistic regression model examining the contribution of multiple factors to mortality in infants and older children using long-term non-invasive ventilation.

	Variables	p value on univariate analysis
Baseline clinical characteristics[a]	▪ Age at NIV initiation (months) ▪ Disease category ▪ Number of co-morbidities	- 0.003 <0.001
Baseline respiratory parameters[b]	▪ Total AHI (events/hr) ▪ Obstructive AHI (events/hr) ▪ Central AHI (events/hr)	<0.001 <0.001 0.022
NIV technology use	▪ Location to start NIV (hospital/home) ▪ Additional technology (yes/no)	<0.001 <0.001
Adherence	▪ Number of hours NIV was used per night (second follow-up visit)	0.021

AHI - apnea-hypopnea index; BPAP – bi-level positive airway pressure; CPAP – continuous positive airway pressure; NIV - non-invasive ventilation

[a] History of upper airway surgeries was excluded from the analysis because of a strong association with the older child age group.

[b] Respiratory parameters such as total sleep time, % of time in rapid eye movement sleep, and % of sleep with $SpO_2 < 90\%$ that were significant on univariate analysis were excluded from the model because of a strong association with the infant age group.

Table 2: Results of binomial logistic regression with mortality as the outcome variable and population characteristics and technology use as covariates.

	B ± SE	p Value	Exp(B)	95% C.I. for Exp(B)
Additional technology	3.254 ± 1.201	0.007	25.905	2.460 to 272.849
Constant	-4.546 ± 1.688	0.007	0.011	

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