Long-term non-invasive ventilation in children

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Use of long-term non-invasive ventilation is increasing exponentially worldwide in children of all ages. The treatment entails delivery of ventilatory assistance through a non-invasive interface. Indications for use of non-invasive ventilation include conditions that affect normal respiratory balance (eg, those associated with dysfunction of the central drive or respiratory muscles) and disorders characterised by an increase in respiratory load (eg, obstructive airway or lung diseases). The type of non-invasive ventilation used depends on the pathophysiological features of the respiratory failure. For example, non-invasive ventilation will need to either replace central drive if the disorder is characterised by an abnormal central drive or substitute for the respiratory muscles if the condition is associated with respiratory muscle weakness. Non-invasive ventilation might also need to unload the respiratory muscles in case of an increase in respiratory load, as seen in upper airway obstruction and some lung diseases. Technical aspects are also important when choosing non-invasive ventilation—eg, appropriate interface and device. The great heterogeneity of disorders, age ranges of affected children, prognoses, and outcomes of patients needing long-term non-invasive ventilation underline the need for management by skilled multidisciplinary centres with technical competence in paediatric non-invasive ventilation and expertise in sleep studies and therapeutic education.

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Introduction

Long-term non-invasive ventilation entails delivery of ventilatory assistance through a non-invasive interface, as opposed to invasive ventilation via tracheostomy. The number of children treated at home with this type of respiratory support is increasing exponentially around the world.[1–3] Some evidence suggests mortality is decreased with non-invasive ventilation, but the main benefit of the treatment is indisputably better family experience and health-related quality of life.[2,4–7] However, the increase in use of non-invasive ventilation contrasts with the shortage of validated criteria for initiation and the scant proven physiological benefits.[8]

There are two main types of non-invasive ventilation. First, continuous positive airway pressure (CPAP) delivers a constant positive pressure to the airways and aims to maintain airway patency throughout the entire breathing cycle. Second, biphasic positive airway pressure (BiPAP) aims to assist the breathing of the patient by delivering a supplemental higher positive pressure during every inspiration.

In this Review, we summarise paediatric disorders that might benefit from long-term non-invasive ventilation and discuss indications and expected and proven benefits. Further, we describe available equipment and detail the follow-up and monitoring of patients. Finally, we conclude with questions about ethics of non-invasive ventilation and areas for future research.

Paediatric disorders that might benefit from non-invasive ventilator support

Non-invasive ventilation is indicated for disorders that cause disequilibrium in the respiratory balance. Components of respiratory balance are the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive (figure). In healthy people, the respiratory load—ie, the effort the individual has to exert to generate a breath—is low, the capacity of the respiratory muscles is normal, and the central drive appropriately commands the respiratory muscles (figure A). In disorders characterised by an increase in respiratory load, or by a weakness of the respiratory muscles, the central drive increases its demands on the respiratory muscles (figure C). When this imbalance exceeds a certain threshold, hypoventilation (defined by hypercapnia and hypoxaemia) occurs. Severe upper airway obstruction, airway malacia, and advanced lung diseases (eg, cystic fibrosis, bronchopulmonary dysplasia, or bronchiolitis obliterans) might account for an excessive respiratory load (panel 1).[9–15] Neuromuscular diseases that involve the motor neuron, the peripheral nerve, the neuromuscular junction, or the respiratory muscles can cause respiratory muscle weakness. Chest wall disorders (eg, kyphoscoliosis) could be associated with an increase in respiratory load and dysfunction of the respiratory

Key messages

- Use of non-invasive ventilation is increasing exponentially worldwide in children of all ages
- Increased use of non-invasive ventilation contrasts with scant validated criteria for initiation of the treatment and few proven benefits
- Continuous positive airway pressure (CPAP) is not appropriate for treatment of sleep-disordered breathing in children with neuromuscular disease, and biphasic support (BiPAP) should be used when non-invasive ventilation is implemented in these patients
- Technical aspects of non-invasive ventilation—eg, interface and device—are crucial when choosing non-invasive ventilation
- Training of caregivers and patients and organisation of adapted home care are essential
- Heterogeneity of disorders, ages of affected children, prognosis, and outcomes of patients all underline the need for management by skilled paediatric multidisciplinary centres

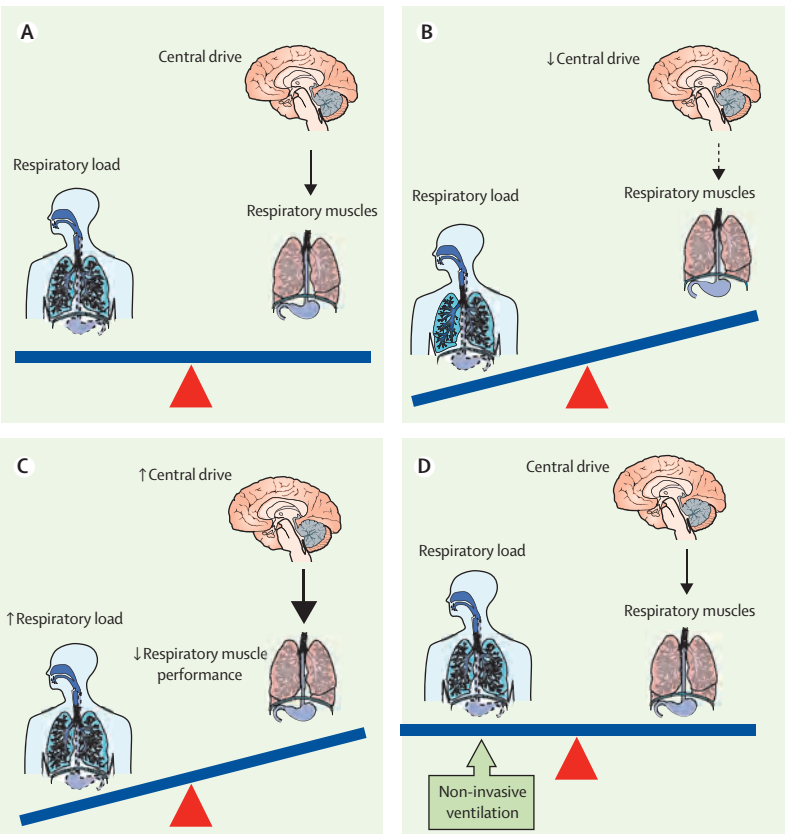

Figure: **Respiratory balance**
(A) Normal respiratory balance is when the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive are in equilibrium. (B) A decrease in central drive (dotted line) causes a decrease in the activity of the respiratory muscles and, subsequently, a reduction in alveolar ventilation. (C) A weakness of the respiratory muscles or an increase in respiratory load causes an increase in central drive (bold arrow). Alveolar ventilation occurs when the imbalance exceeds a specific threshold. (D) Non-invasive ventilation can correct disequilibrium in the respiratory balance by replacing central drive, unloading (in case of an increase in respiratory load, as shown), or assisting the respiratory muscles (in case of respiratory muscle weakness).

Panel 1: **Examples of disorders that can cause disequilibrium in the respiratory balance**

Increase in respiratory load

Anatomical abnormalities of the upper airway
- Treacher Collins syndrome
- Craniofaciostenosis
- Pierre Robin syndrome
- Pycnodysostosis
- Achondroplasia
- Tracheomalacia or laryngomalacia
- Congenital or acquired laryngotracheal stenosis
- Vocal cord paralysis
- Other upper airway malformation
- Storage diseases
- Neck masses or tumours
- Down's syndrome
- Beckwith-Wiedemann syndrome

Lower airway obstruction
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Bronchiolitis obliterans

Decrease in performance of respiratory muscles
- Spinal muscular atrophy
- Spinal cord injury
- Phrenic nerve injury
- Myasthenia
- Myopathies and dystrophies

Dysfunction of central drive
- Congenital central hypoventilation syndrome
- Brain injury by tumours or infection (encephalitis)
- Brainstem dysfunction (eg, Chiari malformation)

muscles, with the respiratory muscles having a mechanical disadvantage because of distorsion of the chest wall. Disorders of the central drive are rare and could be congenital (eg, congenital central hypoventilation syndrome [Ondine's curse]) or acquired due to compression of or injury to the brainstem. Other disorders involving an impairment of two or more components of respiratory balance (eg, achondroplasia and mucopolysaccharidoses) can cause upper airway obstruction and brainstem compression.

The type of non-invasive ventilation needed by patients depends on the pathophysiological features of their respiratory failure. CPAP is the simplest type of non-invasive respiratory support and is indicated in cases of isolated obstruction of the upper or lower airways. Indeed, in the case of airway obstruction causing an increase in respiratory load, the two other components of respiratory balance (ie, the respiratory muscles and central drive) are unaffected, and restoration of sufficient airway patency throughout the entire breathing cycle normalises breathing (figure D).[9,12] BiPAP is indicated when these two other components of respiratory balance are also impaired.

In lung diseases associated with an increase in respiratory load, the aim of non-invasive ventilation is to unload the respiratory muscles.[10,11,14,16] Since affected individuals have a normal central drive and preserved respiratory muscle capacity, ventilatory assistance that maintains the patient's own breathing pattern by allowing them to trigger assisted breaths will be the most appropriate and comfortable.[10,11] Conversely, in individuals with weak respiratory muscles, the role of BiPAP will be to assist or replace, according to the severity of the weakness, the respiratory muscles by delivering positive pressure during inspiration. For these patients, triggering of the ventilator might be difficult or impossible. A controlled mode with a back-up rate (ie, a minimum number of breaths delivered per min by the ventilator) close to the normal respiratory rate during sleep for age is recommended. Thus, CPAP is clearly not the treatment for sleep-disordered breathing in patients with neuromuscular disease. Finally, in individuals with an

abnormal central drive, the BiPAP ventilator should be able to take over command of the respiratory muscles by means of a controlled mode.

Equipment and settings for non-invasive ventilation

Equipment for non-invasive ventilation comprises the interface, the circuit, and the device. Important improvements have been made in interfaces available for children (table). Interfaces can cover the nose (nasal mask), the nose and the mouth (nasobuccal mask), the face (total face mask), and, exceptionally, the mouth only (mouthpiece).[17,18] Nasal pillows (or prongs or cannulas) are minimum contact interfaces that are available for children aged 5–7 years or older and are very well tolerated.[17]

Interfaces can be either vented or non-vented. Vented interfaces incorporate intentional leaks and are to be used with a single circuit (ie, with only an inspiratory line, the expiration occurring through the intentional leak on the interface) and a minimum positive expiratory pressure. Non-vented masks can be used with a double circuit (ie, with a separate inspiratory and expiratory line) or a circuit with an expiratory valve (ie, with only an inspiratory line, the expiration occurring through a valve that opens exclusively during expiration), with or without positive expiratory pressure. A minimum level of expiratory pressure is mandatory for vented masks, to allow the clearing of carbon dioxide during expiration.[19,20]

The choice of interface is decided by the patient's age, weight, facial and skull anatomy for the fitting of the headgear, nasal permeability and the eventual presence of mouth breathing, ventilatory mode (requiring a vented or non-vented interface), comfort and tolerance with the interface, and the patient's ability and need to remove the interface unaided. Nasal masks and full face masks are also available for neonates and infants, which have contributed to the rapid expansion in use of non-invasive ventilation in young children.[21] Children with maxillofacial deformities—eg, those with Treacher Collins syndrome—will generally need a nasobuccal mask.[22]

Different modes of non-invasive ventilation are available. Constant CPAP is the simplest mode and has proven efficacy in children with severe upper airway obstruction.[9,12,15,23–25] Autotitrated CPAP is a mode during which positive airway pressure is adjusted automatically between a minimum and maximum airway pressure set by the prescriber, according to analysis of the flow curve and airway resistance by device software. More advanced modes—associated with a moderate decrease in airway pressure at the onset of expiration, or a variable increase in airway pressure during inspiration—are also available.[26] Since all CPAP devices have been designed for adult patients, manufacturers recommend a minimum weight, usually between 10 kg and 30 kg, for use of the autotitrated and advanced CPAP modes. A few studies have compared constant CPAP with autotitrated and advanced CPAP modes, but superiority of these more complex modes has not been shown with respect to comfort or efficacy, compared with constant CPAP.[27,28]

The aim of CPAP titration is to suppress any residual respiratory event and is usually done during polysomnography.[29] Titration might also be done by means of recording oesogastric pressures, which reflect the inspiratory and expiratory work of breathing. In infants with severe upper airway obstruction, setting the CPAP pressure to the highest tolerated pressure is recommended, because a setting based on non-invasive clinical variables (eg, improvement in oxygenation and CO_2 levels, reduction in respiratory rate and heart rate, and increase in tidal volume) has been shown to underestimate the optimum CPAP pressure by a mean of 2 cm H_2O in these patients.[15]

During BiPAP, a higher level of positive pressure is delivered during inspiration by means of a volume-targeted or pressure-targeted mode. With volume-targeted ventilation, the ventilator delivers a fixed volume throughout a given time span. The advantage of this mode is strict delivery of a preset volume; the main disadvantage is that this mode is not able to adjust to the variable requirements of the patient during sleep—eg, physiological changes in central drive, lung compliance, and airway resistance. Moreover, compensation for unintentional air leaks is not possible, which puts the patient at risk of receiving an insufficient effective inspired volume.[30] With pressure-targeted ventilation, the airflow is adjusted to generate a constant positive pressure during a given time span. The

	Advantages	Disadvantages	Side-effects
Nasal mask	Small internal volume; large choice of different industrial models	Not usable in case of mouth leaks	Pressure sores, eye irritation if leaks, facial deformity
Nasobuccal mask	Prevents mouth leaks	Large volume; risk of inhalation of gastric content in case of gastro-oesophageal reflux; impairs communication and vocalisation; increased aerophagia	Pressure sores, eye irritation if leaks, facial deformity
Total face mask	Prevents mouth leaks	Larger volume than nasobuccal mask; risk of inhalation of gastric content in case of gastro-oesophageal reflux; impairs communication and vocalisation; increased aerophagia	Pressure sores, facial deformity
Nasal pillows	Small and light; no pressure sores	Not usable in case of mouth leaks	Nasal irritation
Mouthpiece	Small and light; no pressure sores; can be used intermittantly	Not useable during sleep	None

Table: **Advantages, disadvantages, and side-effects of interfaces for children**

delivered volume depends on the interaction between the preset pressure, the patient's inspiratory effort, and the respiratory mechanics.[31] The main advantage of pressure-targeted ventilation compared with volume-targeted ventilation is its ability to compensate for unintentional leaks. Patient–ventilator synchronisation is improved because flow can vary on a breath-to-breath basis. However, this mode requires that the device is able to detect the onset and end of inspiration of the patient, which can be difficult in young children because of small airflows and volumes.[12] Innovative modes, also called hybrid modes, use intelligent algorithms to adjust one or more settings automatically to achieve predefined targets.[32] These hybrid modes, known as volume-targeting pressure ventilation (VTPV) or average volume-assured pressure support (AVAPS), combine the characteristics of both volume-targeted and pressure-targeted ventilation to overcome previous limitations. These modes provide a predetermined target volume while maintaining the physiological benefits of the pressure-targeted mode. The ventilator measures or estimates the volume of each expired breath and adjusts inspiratory pressure automatically within a predetermined range to ensure a stable target volume. Hybrid modes are used increasingly in paediatric patients despite scarcity of validated studies in children.[33]

BiPAP settings should be adjusted to the patient's underlying disorder. In children with neuromuscular disease, the aim is to deliver a physiological tidal volume. This goal can be achieved with low inspiratory pressures in young infants with compliant lungs and chest wall, but higher inspiratory pressures will be necessary in older children, those with scoliosis, or patients who are obese. Expiratory pressures should be set at the lowest values, because patients with neuromuscular disease usually have no airway obstruction. A back-up rate close to the physiological breathing rate during sleep is recommended; inspiratory triggering of the ventilator can be difficult for a child with weakened respiratory muscles and, therefore, a back-up rate is needed to avoid apnoea. In children with cystic fibrosis, the optimum settings for non-invasive ventilation have been assessed in physiological studies measuring the work of breathing.[10,11,16] In these patients, the optimum mean inspiratory pressure was 16 cm H_2O with no expiratory pressure, the inspiratory trigger should be sensitive, and a back-up rate is recommended to avoid apnoea.[11,16] In other lung diseases (eg, bronchiolitis obliterans), a high level of expiratory pressure might be necessary to counterbalance the intrinsic positive end-expiratory pressure.[14] In any case, settings for CPAP or BiPAP should be set and adapted individually.

Negative pressure ventilation comprises the application of negative pressure around the chest during inspiration, to expand the thorax and generate a tidal volume. This method has been used for several decades, mainly in adult patients with neuromuscular disease, and its use in children is limited.[5] However, use of negative pressure ventilation has expanded during the past few years because devices have improved greatly in performance and have become smaller. This type of ventilation could be worthwhile at night or for patients who cannot tolerate a non-invasive interface. However, the biggest problem with use of negative pressure ventilation is that of obstructive sleep-disordered breathing due to suppression of the normal preinspiratory activation of upper airway muscles. The effectiveness of this approach should, therefore, be checked carefully because of the risk of persistent respiratory events and desaturations.[34]

Indications for and benefits of non-invasive ventilation

No criteria have been validated for when to start long-term non-invasive ventilation in children. In clinical practice, non-invasive ventilation can be initiated in several situations: in an acute setting; after failure to wean a patient off non-invasive ventilation in the paediatric intensive care unit; in cases of abnormal nocturnal gas exchange alone; or in patients with a high apnoea-hypopnoea index on polysomnography.[8] The main challenges or difficulties for initiation of non-invasive ventilation in children are: deciding on the timing and type of investigation that should be done (eg, polysomnography, polygraphy, or an overnight gas exchange recording); and defining the values or thresholds of variables that are retained (eg, the oxygen or CO_2 level, or the apnoea-hypopnoea index) with the assumption that their correction will be associated with a benefit of non-invasive ventilation.[8] These difficulties are attributable to the paucity of markers for end-organ morbidity associated with sleep-disordered breathing and chronic respiratory failure in children. Neurocognitive dysfunction and behavioural disturbances are the most common and severe outcomes of obstructive sleep apnoea in children, but these deleterious effects are highly variable from one child to another.[35] Of note, morbidity associated with sleep-disordered breathing has been studied little in children needing non-invasive ventilation for disorders other than obstructive sleep apnoea.

A sleep study forms part of the routine assessment for a child with obstructive sleep apnoea. Polysomnography represents the gold standard, but polygraphy or continuous monitoring of nocturnal gas exchange by measurement of pulse oximetry (SpO_2) and transcutaneous partial pressure of CO_2 ($PtcCO_2$) can be used as an alternative procedure if full polysomnography is not available.[36] Usual indications for CPAP are residual obstructive sleep apnoea after adenotonsillectomy (defined as an apnoea-hypopnoea index greater than five events per h) and obstructive sleep apnoea related to obesity or craniofacial abnormalities.[36] Every therapeutic intervention in a child with obstructive sleep apnoea should be evaluated after 6 weeks to 12 months. In practice, CPAP is prescribed in children with complex

obstructive sleep apnoea due to anatomical or structural abnormalities of the upper airways—eg, craniofacial malformations, Down's syndrome, Prader-Willi syndrome, or morbid obesity.[6,37,38] BiPAP is indicated if nocturnal hypoventilation persists despite optimum CPAP.[36] CPAP is associated with an improvement in sleep variables—eg, the apnoea-hypopnoea index, gas exchange, attention deficits, behaviour, sleepiness, and quality of life.[6]

Less consensus exists about the type of investigation and criteria for initiation of BiPAP in children with neuromuscular diseases. First, BiPAP might be justified without a sleep study when the child presents with episodes of acute respiratory failure triggered by a respiratory infection or an anaesthetic procedure, since these events are markers of insufficient respiratory reserve.[39] Concerning the timing of a sleep study, validated recommendations are sparse, possibly because of the heterogeneity of neuromuscular disorders in children and the variability of respiratory involvement within a specific disease—eg, spinal muscular atrophy or collagen 6 (COL6) myopathies.[40,41] Symptoms suggestive of sleep-disordered breathing did not differ in children with a neuromuscular disorder with or without overt nocturnal hypoventilation.[42] These symptoms, therefore, cannot be used as predictors or markers of nocturnal hypoventilation; moreover, they can be difficult to assess in young children and typically arise too late in the course of the disease to be of diagnostic value. With respect to the predictive value of lung function and other respiratory variables, researchers on a large prospective study of children with neuromuscular disorders did not identify a sensitive and specific daytime lung function or respiratory muscle test that was associated with or predictive of nocturnal hypoxaemia or hypercapnia.[43] The type of neuromuscular disorder should be taken into account, because nocturnal hypoventilation occurs more often in disorders characterised by prominent diaphragmatic weakness. Children with a COL6 myopathy should be screened systematically for sleep-disordered breathing.[44] Prioritised screening is also recommended for infants or young children with congenital myopathies or rapidly progressive neuromuscular diseases.[45] In children with neuromuscular disease, documentation of nocturnal hypoventilation by means of polysomnography is recommended but not essential before starting BiPAP, because isolated abnormal nocturnal gas exchange can be sufficient to show hypoventilation and justify BiPAP initiation.[46] Indeed, nine of ten patients with neuromuscular disease or thoracic deformity and isolated nocturnal hypercapnia without daytime hypercapnia progressed to overt daytime respiratory failure within a period of 2 years.[46] Moreover, in the presence of an abnormal overnight gas exchange recording or full polysomnography, criteria that are used to define nocturnal hypoventilation are highly variable, which has practical outcomes because an indication for long-term non-invasive ventilation relies on detection of hypoventilation.[47] The scoring of polysomnography in patients with neuromuscular disease needs specific expertise. Indeed, instead of apnoeic and hypopnoeic events, patients can present with a progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of global inspiratory muscle weakness.[48] Paradoxical breathing with opposition phase on the thoracic and abdominal belts can be a result of diaphragmatic dysfunction or weakness of the intercostal muscles and should not be interpreted falsely as obstructive events.[48–50]

Periods of reduced ventilation or paradoxical breathing (more so than obstructive or central apnoea-hypopnoea, particularly during rapid-eye movement sleep), which are associated with SpO_2 less than 90% or $PtcCO_2$ greater than 50 mm Hg, are indicative of insufficient respiratory muscle performance and justify long-term BiPAP in children with neuromuscular disease. In clinical practice, however, many children with a progressive neuromuscular disease (eg, spinal muscular atrophy or Duchenne muscular dystrophy) are started on non-invasive ventilation empirically. Indeed, limited access to sleep studies should not delay these patients accessing an effective treatment, the most important requisite being that children should be followed up by a paediatric team with expertise in non-invasive ventilation.

Widespread use of BiPAP in children with neuromuscular disease contrasts with the few studies in which the benefits of BiPAP have been assessed in children. Findings of studies in small numbers of patients show that BiPAP is associated with normalisation of nocturnal and daytime gas exchange, an improvement in sleep quality, and a reduction in symptoms associated with sleep-disordered breathing.[51–53] Non-invasive ventilation associated with mechanical insufflation-exsufflation, prevents thoracic deformities and consequent thoracic and lung hypoplasia in young children with neuromuscular disease.[54] Intermittent positive-pressure breathing, which entails delivery of high inspiratory pressures generally on a daily basis during daytime, can increase ventilation in patients with neuromuscular disease.[55] Both non-invasive ventilation and intermittent positive-pressure breathing are also effective at prevention of atelectasis and the risk of pneumonia in children with neuromuscular disease.[56]

Children with cystic fibrosis do not have a validated indication for a sleep study or BiPAP. In a prospective multicentre study of 80 paediatric and adult patients with stable cystic fibrosis, who had a forced expiratory volume in 1 s (FEV_1) less than 60% predicted, 13 (18%) patients spent more than 10% of night-time with SpO_2 less than 90% and 33 (47%) had $PtcCO_2$ greater than 45 mm Hg.[57] Nocturnal gas exchange correlated with daytime arterial blood gases, and nocturnal SpO_2 correlated with FEV_1. However, no correlation was recorded between the

subjective assessment of sleep quality (by means of questionnaires) and the objective evaluation of nocturnal gas exchange. No consensus exists about clinical situations or criteria that justify initiation of BiPAP in children with cystic fibrosis. Similar to adult patients with chronic obstructive pulmonary disease, BiPAP is recommended as a first-line treatment for an acute hypercapnic respiratory exacerbation, without any evidence from prospective randomised studies.[58–60] BiPAP is also prescribed largely for patients on lung transplant lists and those with insufficient improvement after oxygen therapy.[61] This usage contrasts with the conclusion of a Cochrane review, in which improvement of nocturnal gas exchange and diminished oxygen desaturation and respiratory muscle fatigue during chest physiotherapy were the only proven benefits of BiPAP in cystic fibrosis.[62] An unresolved question is the use of non-invasive ventilation for CO_2 clearance in children with pulmonary hypertension due to primary lung or complex congenital heart disease; children with congenital heart disease are a burgeoning population with high-risk home needs.

In clinical practice, non-invasive ventilation is associated with improved feeding, weight gain, and growth, which supports findings of physiological studies showing that non-invasive ventilation decreases the work of breathing and resultant caloric burn.[9,63] In some studies, non-invasive ventilation was also associated with improved sleep quantity and quality, which has a positive effect on neurocognitive and behavioural outcomes.[6,64]

Screening with at least an overnight gas exchange recording to detect nocturnal hypoxaemia or hypercapnia, and if possible with a complete sleep study, should be a priority in all children with upper airway obstruction and any type of neuromuscular or lung disease that might be associated with nocturnal hypoventilation. Symptoms of sleep-disordered breathing are insufficiently sensitive and specific and tend to arise late in the course of the different diseases. Since poor sleep quality is associated with neurocognitive dysfunction, abnormal behaviour, and decreased quality of life, a trial of 1–3 months of non-invasive ventilation with a thorough assessment before and after the period of non-invasive ventilation, seems a reasonable option.

Practical follow-up of children

Non-invasive ventilation is a technically challenging treatment, but the ultimate aim is to perform it at home. It is usually initiated in hospital during a short admission, to acclimatise the patient to their treatment. Because non-invasive ventilation will be administered during sleep, overnight monitoring of sleep with the optimum settings—at least with an assessment of overnight gas exchange and ideally with polygraphy or polysomnography—is recommended before discharge. However, non-invasive ventilation might also be implemented in the home care setting, according to local resources, family capacity, patient's stability, and other socioeconomic factors. Because of a shortage of hospital beds at our institution (Hôpital Necker Enfants-Malades, Paris, France), we have started outpatient initiation of non-invasive ventilation for selected patients, with efficacy and compliance comparable with in-hospital initiation (unpublished data). A sleep study with non-invasive ventilation is recommended but can be postponed until the patient is well adapted to their treatment and is able to sleep at least 6 h with the device. Training of caregivers and the patient is essential. Caregivers must not only be familiar with putting on and taking off the interface and device but also must have training for the different problems that might arise at home.[65] Careful checking of the caregiver's competence is mandatory. Availability of a trained home care provider, who is able to visit the patient at home on a regular as-needed basis, is an important requisite of success for outpatient initiation. However, the large variability in availability and quality of home care nursing to buttress parental care remains a limitation of home non-invasive ventilation in children.

Compliance with non-invasive ventilation is a major issue, because treatment efficiency is related to length of nocturnal use.[6] In most studies, fairly low compliance has been reported, with mean night-time use between 3 h and 5 h.[6,27,28] However, objective compliance close to the recommended sleep duration in children can be achieved by expert centres having a specific non-invasive ventilation therapeutic education programme.[66] Close collaboration is necessary between the hospital team and the home care provider. Home care provider systems vary from one country to another, but the team visiting the patient at home must have expertise in paediatric non-invasive ventilation. Caregivers should be able to contact the home care provider for any technical assistance and the hospital team for any medical issue at any time.[65]

No validated guidelines are available for monitoring or long-term follow-up of children undergoing non-invasive ventilation. Timing of follow-up visits depends on the age and medical condition of the child. At our institution, we undertake a sleep study in hospital 1 month after initiation of non-invasive ventilation, then have at least one outpatient follow-up visit and one in-hospital full sleep study with non-invasive ventilation every 2–6 months. However, practice at other institutions and in other countries varies, with no evidence for superiority of one approach over another. However, overnight measurement of SpO_2 with $PtcCO_2$ recording during non-invasive ventilation usually takes place at every follow-up visit because many asymptomatic patients remain hypercapnic during sleep with non-invasive ventilation, despite a normal overnight SpO_2 and normal daytime blood gases.[67] This residual nocturnal hypercapnia can be corrected easily by simple measures—eg, changing the interface or the ventilator settings.[67] Check-ups can also be done at home with adequate training of staff.[68] Simultaneous

analysis of the in-built software of the ventilator and the overnight gas exchange gives useful information on important issues such as objective compliance, unintentional leaks, respiratory rate, airway pressure, and respiratory events. However, because most devices are designed for adults, this information is not always reliable for children.[69] Systematic polygraphic studies are recommended during non-invasive ventilation because residual respiratory events—eg, patient–ventilator asynchronies, unintentional leaks, persistent obstructive events with or without reduction in central drive, and persistent central or mixed events—are common in asymptomatic children with stable disease and might be accompanied by desaturations or arousals.[70,71] Residual respiratory events are less common in asymptomatic children with stable disease after treatment with CPAP.[38]

Compared with most adult patients, a substantial number of children could be weaned off their ventilator support over time.[2] Indeed, some conditions (eg, Pierre Robin syndrome or bronchopulmonary dysplasia) improve spontaneously with increasing age.[21,63] Other disorders, such as tracheal or laryngeal stenosis, Treacher Collins syndrome, or craniofaciostenosis, might improve after upper airway surgery, maxillofacial surgery, or neurosurgery. No recommendations or guidelines are available for weaning children off ventilator support. Depending on the type of corrective surgery, a minimum delay of about 2–6 months is typical for weaning off non-invasive ventilation, corresponding to the timing associated with the maximum benefit of the surgical intervention. In the case of spontaneous improvement, a sleep study without CPAP or non-invasive ventilation is indicated at least 2–4 weeks after weaning off ventilator support because of the long-lasting effects of CPAP and non-invasive ventilation. In any case, long-term follow-up is recommended because of the possibility of recurrence of sleep-disordered breathing.[72]

Side-effects, limitations, and ethical aspects

Non-invasive ventilation can be associated with side-effects (table). The most common are those caused by the interface and include skin injury from pressure sores, eye irritation because of unintentional air leaks, and facial deformity in young patients.[73] Skin injury is less common than several years ago because of improvements in interfaces for children and the use of minimum contact interfaces such as nasal pillows. Mouth leaks can be minimised by use of a chin strap or a pacifier in infants, or a change to a nasobuccal mask. Facial flattening and maxillary retrusion can be prevented by use of nasal pillows or by alternating different interfaces—eg, a nasal mask and a nasobuccal mask. Other side-effects might be attributable to the positive pressure. Aerophagia or gastric distension, and increased gastro-oesophageal reflux, can be seen with high CPAP pressures or, in case of patient–ventilator asynchrony, with BiPAP. These abdominal side-effects can be managed by decreasing the airway pressures or correcting patient–ventilator asynchrony. Autonomic arousals might be seen during persistent obstructive events with CPAP and during unintentional leaks with BiPAP.[8,71]

Non-invasive ventilation still has some limitations in the youngest children. A minimum weight of 5 kg is generally recommended as a cutoff for this treatment in the community. However, recommendations vary by country and, most importantly, these cutoffs have not been validated clinically.

Sleep affects the three components of the respiratory balance: respiratory load, the respiratory muscles, and central drive (figure). Physiological changes in respiratory and upper airway function, respiratory muscle power, and ventilatory response lead to reduced ventilation during sleep. Most patients need non-invasive ventilation only during sleep,[1,2] but some patients will also need this treatment during the daytime, particularly individuals with advanced neuromuscular disease.[74,75] In children with neuromuscular disease, mouthpiece ventilation during the daytime can prolong the duration of non-invasive ventilation and delay the timing of a tracheostomy.[74–76] In a study of 30 adult patients with neuromuscular disease, patient-reported benefits of mouthpiece ventilation included a reduction in dyspnoea and fatigue and an improvement in speech and eating.[75] However, mouthpiece ventilation can be impossible or difficult in very young children. Even if non-invasive ventilation is very effective, it can be difficult to apply around the clock on a long-term basis. Some expert teams have had successful experiences with non-invasive ventilation in children with neuromuscular disease who are totally dependent on a ventilator.[77] Other clinicians consider that the child should be able to breathe spontaneously without non-invasive ventilation for a minimum time per day so they can be discharged home safely. However, this practice is also dependent on local experience and patient's preference. A tracheostomy represents a possible option for children with a progressive neuromuscular disease, which has to be prepared and discussed thoroughly with the child and their parents. However, this invasive procedure is not always associated with a decrease in quality of life.[78]

The decision to transition to tracheostomy is complex for children with severe underlying disease with a fatal outcome and rapid decline, developmental delay, or severe physical or cognitive disabilities. Determining the best interests of the child is important, and the Royal College of Paediatrics and Child Health states that the decision must balance the "benefits and burdens of treatment and outcomes, whilst considering ascertainable wishes, beliefs and values and preferences of the child and their family, the cultural and religious views of the matter, the views of those providing care for the child and what choice is less restrictive for future options".[79] The transition from non-invasive ventilation to tracheostomy can be associated with a great burden

Panel 2: Goals for future studies of long-term non-invasive ventilation in children

- Investigation of the correlation between clinical scenarios, symptoms, and physiological respiratory variables used for initiation of long-term non-invasive ventilation and outcomes
- Validation of criteria for weaning off long-term non-invasive ventilation
- Better understanding of neurocognitive and behavioural benefits of non-invasive ventilation in children with disorders other than obstructive sleep apnoea
- Validation of the optimum follow-up for children treated with long-term non-invasive ventilation

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and relevant specialty journals for articles published between Jan 1, 1980, to Jan 1, 2016, with the terms: ("noninvasive ventilation", "noninvasive ventilatory support", "noninvasive mechanical ventilation", "positive pressure ventilation", "continuous positive airway pressure", "bilevel ventilation", "BiPAP", OR "negative pressure ventilation") AND ("pediatric", "children", OR "infants"). We selected publications from 2004 to 2016, with an emphasis on those published after 2011, but we did not exclude commonly referenced and highly regarded older publications. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged relevant. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports.

with respect to the improvement in quality of life of the child and their family.[80] Non-invasive ventilation might then be used as part of a palliative care approach, without prolonging excessively a poor or unbearable quality of life. The confidence, transparency, and quality of the relationship of the family with the health-care team are of crucial importance and determine the individual nature of these decisions. However, this area of health-related quality of life remains complex and is evolving.[81–84]

Concluding remarks

Long-term non-invasive ventilation is a very effective type of respiratory support that has transformed the scope of chronic respiratory failure and severe sleep-disordered breathing in children by avoiding tracheostomies and allowing patients to live at home with a good quality of life for themselves and their families. The great heterogeneity of disorders, patients' ages, prognosis, and outcomes underline the need for management by skilled multidisciplinary centres having technical competence in paediatric non-invasive ventilation and expertise in sleep studies and therapeutic education. The increased use of non-invasive ventilation contrasts with the scant proven benefits. Future studies should aim to define disease and age-appropriate initiation and weaning criteria, and objective physiological and quality of life benefits (panel 2).

Contributors

BF wrote the Review, with contributions from AA and AF. All authors approved the final version.

Declaration of interests

We declare no competing interests.

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