PEDIATRIC LONG-TERM NON-INVASIVE VENTILATION

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PEDIATRIC LONG-TERM NON-INVASIVE VENTILATION

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EDITORIAL
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Editorial: Pediatric Long-Term Non-invasive Ventilation

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Keywords: OSAS (obstructive sleep apnea syndrome), obesity, cystic fibrosis—CF, CPAP (continuous positive air pressure), BiPAP (bilevel positive airway pressure), neuromuscolar disorders, palliative care—methods, long term non-invasive ventilation

Editorial on the Research Topic

Pediatric Long-Term Non-invasive Ventilation

Long-term non-invasive mechanical ventilation consists in the delivery of non-invasive mechanical ventilation (NIV) at least 6 h per day for more than 3 weeks (1). Long term NIV is increasing world-wide, with broader indications, and is associated with an increase in survival rate in children with chronic conditions. In this Research Topic different experts in the field deepen the topic of long-term NIV in children.

Praud reviewed the current use of home NIV. He focused on the advantages of long-term home NIV compared to prolonged hospitalization and to home invasive ventilation in different countries. He reported interesting data of two scoping reviews about this topic (2, 3). In addition, Basa et al. have brought to the topic their experience in a middle-income country. Their experience could be considered as a model of setting up a home mechanical ventilation center: since 2001 the number of patients on ventilation has increased rapidly. They reported their numbers and their high proportion of invasively ventilated patients (about a half of the patients). As can be seen from other works in literature, the increase in NIV experience is associated with a reduction of invasively ventilated patients (4).

Certainly, NIV is increasing its popularity in the last few years due to its relative simplicity. However, technical knowledge of machines, interfaces, circuits as well as indications is required. Ferreira deepened the topic of interfaces and circuits. NIV is usually well-tolerated but may be associated with some side effects. An experienced team confident with tricks and possible complications related to NIV is crucial to avoid NIV failure. Main adverse events are discomfort, skin lesions, unintentional leaks, or disturbed facial growth (midface hypoplasia). On the one hand, skin lesions and unintentional leaks may be reduced by changing interface periodically, using protective dressings and selecting the appropriate mask type. On the other hand, discomfort may be reduced using active humidification finally improving adherence (5, 6). Pavone et al., provided a comprehensive report of different ventilators available on the market and the different ventilatory modes. Nowadays, new hybrid modes are flanking the traditional pressure-target and volume-target modes. Hybrid modes require more studies in pediatrics but the small literature available shows that they may reduce asynchronies and facilitate management of children poorly adapted to traditional modes (7). Moreover, new ventilators are equipped with built-in software and allow remote monitoring of ventilation parameters: these data supply information about trends of patients on home ventilation and are useful for the clinician to understand possible causes of suboptimal ventilation (8). It is evident that new technologies are constantly improving information given to clinicians about home NIV. Those new possibilities are changing type of

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follow-up of children at home giving. Nowadays, ventilators provide many information, often accessible remotely, and the clinician can monitor ventilator trends easily and without requiring hospitalization. Khirani et al. provided a comprehensive analysis of available literature about follow-up of patients on NIV. Unfortunately, there is a lack of validated indications about strategies to monitor patients on CPAP or NIV. However, the authors reported their extensive experience with patients on home CPAP or NIV: type of follow-up is variable depending on the team experience, underlying disease and patient's condition. Certainly, CPAP and NIV require a regular assessment with a minimum time (1–3 months after first adaptation and reassessment every 6–12 months) (9). Monitoring should include ideally a P(S)G [poly(somno)graphy] or nocturnal pulse oximetry (SpO_2) and capnography (CO_2) recording, if P(S)G is not available. As stated above, monitoring of home patients has been improved during the last few years with new tools such as telemedicine and analysis of data obtained from built-in software. New home ventilators provide useful information on built-in software (adherence, leaks, efficacy of ventilation) representing a useful tool for the clinician for monitoring ventilation. Caution must be taken about interpretation of data as no specific pediatric software is available and there is a lack of standardization of interpretation of data.

As reported by Praud, long-term NIV is increasingly used worldwide, including developing countries, and provides improvements in terms of decreased mortality and increased quality of life. The increased use of NIV in different settings has expanded indications of its use. The use of NIV has been extended in the last few years to patients with bronchopulmonary dysplasia (BPD) requiring long-term respiratory support. Interestingly, despite the paucity of studies to support the use of NIV in patients with cystic fibrosis (CF) and non-CF bronchiectasis, the application of NIV seems to stabilize the decrease of lung function when the disease is advanced (10). Finally, other studies support the use of NIV in patients with bronchiolitis obliterans, making extremely wide the range of possible indications of NIV. Nevertheless, it seems crucial to highlight that in such circumstances an experienced team is required to select carefully patients that may benefit from NIV. Nevertheless, it is crucial to monitor patients in order to evaluate quickly possible NIV failure to change approach accordingly with the main disease. Paglietti et al. reviewed the indication of NIV in children with central hypoventilation (CCHS). In the past, invasive ventilation was the only way to avoid hypoventilation and the subsequent increase of serum carbon dioxide related to the impairment of respiratory drive. The increase of experience in the management of NIV accompanied by the better knowledge of these disorders has meant that an increasing number of children with CCHS has been switched to NIV when feasible (patients requiring ventilation only during sleep). Moreover, decannulation of children with CCHS along with the transition from invasive ventilation to NIV is nowadays to be considered if the patient require only nocturnal ventilatory assistance (11).

The topic goes through the other indications of NIV. Fauroux et al. reported in their paper the most recent evidences about the use of NIV in children with neuromuscular disorders (NMD). Pump failure due to neuromuscular impairment is often an indication of ventilatory support and experience about this topic is increasing worldwide. Therefore, children affected by NMD may experience hypoventilation and this condition could determine mild cognitive impairment, daytime fatigue, poor sleep quality and difficult to carry out normal activities. No validated criteria to start long-term home NIV are available for clinicians, but is currently widely agreed that NIV should be initiated when nocturnal hypoventilation is present, even before the occurrence of symptoms. Therefore, is very important that centers who take care of NMD children are equipped with adequate equipment (polygraphy, SpO_2 and transcutaneous CO_2 monitoring) and experienced professionals to early diagnose nocturnal hypoventilation in order to start and monitor NIV appropriately. However, Fauroux et al. recognized that benefits of NIV in children with NMD are not well-defined: a limited number of studies are available in literature with very small sample size. Nevertheless, NIV showed to be associated with prolonged survival and an improvement in the quality of life in children with Duchenne muscular dystrophy (12) and prolonged survival in children with spinal muscular atrophy type 1 (13). The heterogeneity of disorders, ages and outcomes determines the importance of the correct follow-up for each patient for optimal medical care.

Another of the most represented indication is the use of NIV in children with severe obstructive sleep apneas (OSA). Verhulst reviewed the use of NIV and continuous positive airway pressure (CPAP) in children with obesity and Down syndrome. These children have a high incidence of residual OSAS after adenotonsillectomy (AT) and consequently require additional treatment. CPAP and NIV represent a second level of treatment, when not only adenotonsillectomy has failed, but also weight loss, anti-inflammatory medications and eventual orthodontics treatments are not effective. Interestingly, both those categories of children are affected by low adherence to ventilation and high drop-out rates of therapy. Patients with Down syndrome showed improvement in adherence with time; an alternative in patients with complete intolerance could be high flow nasal cannula as showed by Amaddeo et al. (14).

NIV or CPAP failure requires a multidisciplinary approach considering the underlying diagnosis, comorbidities and eventual alternative treatments (surgery, weight loss, etc.). Amaddeo et al. reviewed possible alternatives to NIV approach in different conditions (NMDs, OSAS, central nervous system diseases etc.). When no treatments are feasible or effective and the ventilatory balance is seriously impaired, invasive ventilation via tracheotomy should be considered. As far as ventilation via tracheostomy is associated with several complications and require a comprehensive multidisciplinary discussion, it represents in many cases a safe management of patients with chronic respiratory failure when no other choices are available. Interestingly, is open the debate about the right choice of ventilation in children dependent to ventilator 24 h per day. If on the one hand, some groups consider NIV feasible, on the other invasive ventilation is considered safe and may improve quality of life when time spent on NIV is too high (15, 16).

Nevertheless, in children with severe underlying diseases, the choice between invasive and non-invasive approach rises to an important ethical dilemma and clinicians must consider all the different aspects in order to choose the better mode of ventilation. Krivec and Caggiano analyzed the use of NIV for palliative purposes. Pediatric palliative care is an emerging field characterized by the difficult balance between prolonged suffering and relief symptoms. Therefore, on the one hand medical and technological advances have made long-term support and survival possible in children with severe chronic health conditions, on the other this may result in prolonging suffering. Authors highlighted the paucity of studies about this actual and crucial topic. They proposed an interesting ethical framework for decision making in pediatric long-term non-invasive ventilation. This approach may provide appropriate room for the interaction between the involved patients, their families, healthcare providers, health authorities and the broader society in order to use NIV to relief symptoms and not to prolong suffering (17).

Another unexpected result of improving medical care is the need to ensure a smooth process of transition to adult care for children with chronic and complex diseases who reach adulthood. Notably, children on long-term NIV are often patients with complex needs with a limited or absent independence. Onofri et al. dealt with this issue providing different care models of transition to adult care used for other chronic pediatric diseases (congenital heart disease, cystic fibrosis, type 1 diabetes mellitus). They discussed barriers and facilitators to the process of health care transition to adulthood. Ideally, the process should be uninterrupted, well-coordinated and comprehensive. However, on the one hand young adults on NIV are vulnerable, prefer pediatric supportive setting and may be scared about the passage to adult healthcare system. On the other hand, adult services may be not familiar with chronic pediatric conditions and adult physicians could lack of experience with patients with poor autonomy. This underestimated and multifaceted issue requires information, education and communication for adolescents, their families and healthcare providers. However, currently no transition model has been shown to be superior to another (18).

CONCLUSIONS

This series offers a comprehensive discussion about main indications, complications, newest evidences and main clinical issues for children on long-term NIV. These reviews written by experts in the field represent a useful tool for clinicians in everyday clinical practice. Moreover, this collection is a worth set of different point of views about different crucial issues for children on NIV and ideas for further researches.

AUTHOR CONTRIBUTIONS

RC and BF contributed equally to the conception and drafting of the editorial. All authors contributed to the article and approved the submitted version.

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REVIEW
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Long-Term Non-invasive Ventilation in Children: Current Use, Indications, and Contraindications

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This review focuses on the delivery of non-invasive ventilation—i.e., intermittent positive-pressure ventilation—in children lasting more than 3 months. Several recent reviews have brought to light a dramatic escalation in the use of long-term non-invasive ventilation in children over the last 30 years. This is due both to the growing number of children receiving care for complex and severe diseases necessitating respiratory support and to the availability of LT-NIV equipment that can be used at home. While significant gaps in availability persist for smaller children and especially infants, home LT-NIV for children with chronic respiratory insufficiency has improved their quality of life and decreased the overall cost of care. While long-term NIV is usually delivered during sleep, it can also be delivered 24 h a day in selected patients. Close collaboration between the hospital complex-care team, the home LT-NIV program, and family caregivers is of the utmost importance for successful home LT-NIV. Long-term NIV is indicated for respiratory disorders responsible for chronic alveolar hypoventilation, with the aim to increase life expectancy and maximize quality of life. LT-NIV is considered for conditions that affect respiratory-muscle performance (alterations in central respiratory drive or neuromuscular function) and/or impose an excessive respiratory load (airway obstruction, lung disease, or chest-wall anomalies). Relative contraindications for LT-NIV include the inability of the local medical infrastructure to support home LT-NIV and poor motivation or inability of the patient/caregivers to cooperate or understand recommendations. Anatomic abnormalities that interfere with interface fitting, inability to protect the lower airways due to excessive airway secretions and/or severely impaired swallowing, or failure of LT-NIV to support respiration can lead to considering invasive ventilation via tracheostomy. Of note, providing home LT-NIV during the COVID 19 pandemic has become more challenging. This is due both to the disruption of medical systems and the fear of contaminating care providers and family with aerosols generated by a patient positive for SARS-CoV-2 during NIV. Delay in initiating LT-NIV, decreased frequency of home visits by the home ventilation program, and decreased availability of polysomnography and oximetry/transcutaneous PCO_2 monitoring are observed. Teleconsultations and telemonitoring are being developed to mitigate these challenges.

Keywords: home ventilation, non-invasive ventilation, neuromuscular disorders, chronic respiratory failure, COVID-19, mouthpiece ventilation

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INTRODUCTION

Advances in perinatal and pediatric critical care have resulted in an increased number of children of all ages with complex medical conditions, including chronic respiratory insufficiency necessitating long-term respiratory support. The latter includes continuous positive-airway pressure (CPAP) and long-term mechanical ventilation. In addition, the use of high-flow nasal cannulae has been recently reported for long-term respiratory support at home in children not amenable to CPAP or mechanical ventilation (1, 2).

Although long-term mechanical ventilation has been variably defined, it is increasingly considered to be the delivery of mechanical ventilation at least 6 h per day for more than 3 weeks (3). Long-term mechanical ventilation can be delivered invasively (via tracheotomy), or non-invasively. Long-term non-invasive ventilation (LT-NIV) is provided via a nasal, oronasal, or facial mask with a bilevel positive airway pressure machine or a portable ventilator. Negative pressure ventilation, which is still mentioned in rare publications on children with acute respiratory failure (4, 5), is virtually absent from recent reports on home long-term ventilation.

This review specifically focuses on LT-NIV, despite the much wider use of long-term non-invasive CPAP at home in children. It describes the worldwide increase in LT-NIV in recent decades and compares the data from various programs around the globe. This is followed by a review and discussion of the indications and contraindications of LT-NIV.

CURRENT WORLDWIDE USE OF LONG-TERM NON-INVASIVE VENTILATION

Pediatric long-term ventilation programs, especially at home, have been increasingly reported since the 1980s in high-income countries as well as those facing more challenging socioeconomic conditions. Long-term home ventilation minimizes disruptions to the child's development and family life, while preventing dependence on institutions. It also avoids nosocomial infections, frees beds in hospitals, and reduces healthcare costs. In Australia, the latter have been reported to be 7 times lower at home than on hospital wards and 25 times lower than in intensive-care units (6). Of note, although several studies have described a better quality of life for the patient on long-term mechanical ventilation at home compared to long-term ventilation in the hospital, this is not always the case for the patient's family. Stress related to emotional difficulties, financial problems, isolation, sleep deprivation, and insufficient resources of the home-ventilation program is indeed rather common (7).

Long-Term Invasive vs. Non-invasive Ventilation for Children at Home

At the same time home-ventilation programs were being developed, an increasing number of children have been put on LT-NIV rather than invasive ventilation in order to prevent tracheostomy-related complications, including acute airway blockade by secretions, accidental decannulation, tracheal injury, and respiratory infections (8). Significant differences in the proportion of children on long-term invasive vs. non-invasive ventilation at home have been reported between countries and centers. The reasons include varying interpretations of the risks of LT-NIV vs. long-term invasive ventilation, the expertise and preferences of the local team, the availability of interfaces for infants and young children, and healthcare costs. **Table 1** lists data on national and local long-term mechanical-ventilation programs in children published in English since 2010. One striking difference between programs relates to the proportion of children on invasive vs. non-invasive ventilation. While half of the studies reported <30% of children on invasive ventilation, the proportion ranges from 0% in one UK center (9) to 75% nationally in the UK (10) and even 98% in Taiwan (11), where nearly all children were hospitalized in dedicated respiratory-care wards. In addition, the proportion of children on invasive ventilation most often was largely under 50% in middle-income countries (12–16). Finally, despite a progressive rise in the use of LT-NIV in infants in their first year of life at initiation of home mechanical ventilation, invasive ventilation via tracheostomy often remains a preferred option at that age, especially due to equipment availability and the frequent need for both nighttime and daytime ventilation (17).

Scoping Reviews on Long-Term Home Non-invasive Ventilation in Infants and Children

Two recent scoping reviews provided comprehensive data on long-term home non-invasive respiratory support internationally.

Castro-Codesal et al. performed a first scoping review of 289 studies on long-term home non-invasive respiratory support—hence including both LT-NIV and CPAP—in children in 2018. The number of children was not specified. The mean age at initiation of long-term non-invasive respiratory support was 8 ± 3 years. The most frequent conditions were upper-airway disorders and neuromuscular diseases. The reported benefits of long-term non-invasive respiratory support at home included decreases in respiratory symptoms, respiratory exacerbations, and postoperative complications, as well as the avoidance of tracheostomy. In addition, polysomnography showed a decrease in the apnea–hypopnea index as well as improved blood gases and sleep architecture (26).

Bedi et al. conducted a second scoping review on both LT-NIV and CPAP involving 60 studies with 977 infants aged 0–2 years in 2018. Respiratory indications included airway disorders (40%), type I spinal muscular atrophy (23%), congenital central hypoventilation syndrome (10%), and various multiple conditions (27%); chronic lung disease of infancy was not mentioned. The authors concluded that infants with airway disorders seemed to benefit from the treatment due to an improvement in respiratory parameters and the potential for outgrowing part of the problem. The only clear benefit at that age, however, was increased survival for infants with spinal muscular atrophy. Results on many outcomes unfortunately were not

TABLE 1 | National and local long-term mechanical-ventilation programs in children published in English since 2010.

Author	Country	No. of patients	Study type	Age at initiation	Main diagnoses	IV/NIV
Tibbals (4)	Australia (2010)	168	Single-center, retrospective, 1979–2008	Median = 6.2 years (range 0.1–19)	• OSA = 32% • NMD = 25% • Tracheobronchomalacia = 14% • Scoliosis = 12% • CNS = 9%	28/30% CPAP: 37%
Racca et al. (7)	Italy (2011)	362	National, cross-sectional, 2007	Median = 8 years (IQR 4–14)	• Musculoskeletal = 49% • Lung/airway disease = 18% • CNS = 13%	41/59%
Wallis et al. (8)	United Kingdom (2011)	933	National, cross-sectional, 2008	—	• NMD = 43% • Lung/airway disease = 37% • CNS = 18%	75/22% §
Paulides et al. (18)	Netherlands (2012)	197	Single-center, retrospective, 1979–2009	Median = 14.7 years (range 0.5–17.9)	• NMD = 66% • CNS = 17% • Lung/airway disease = 6%	51/49%
Hsia et al. (10)	Taiwan (2012)	139 (98% in hospital)	Single-center, retrospective, 1998–2006	Range 0.3–18 years	• CNS = 62% • Lung/airway disease = 13.5% • Genetic anomalies = 11.5% • NMD = 10%	98/2%
Sovtic et al. (19)	Serbia (2012)	29	Single-center, retrospective, 2001–2011	Median = 9.3 years (range 0.5–17.8)	• NMD = 62% • Respiratory/chest/spinal = 38%	40/60%
Amin et al. (11)	Canada (2014)	379	Regional, retrospective, 1991–2011	Median = 9.6 years (IQR: 2.9–13.9)	• Musculoskeletal = 35% • Lung/airway disease = 33% • CNS = 29%	17/83%
Preutthipan et al. (12)	Thailand (2014)	148	Single-center, retrospective, 1995–2012	Mean = 4.6 ± 5.0 years for IV, 9.1 ± 4.4 years for NIV	• OSA = 48% • Lung/airway disease = 17% • NMD = 15%	36/64%
Cancelhina et al. (17)	Portugal (2015)	31	Single-center, retrospective, 1993–2003	Median = 3 years (range 0–13)	• NMD = 39% • Metabolic disease = 23% • CNS = 19%	19/81%
Chatwin et al. (13)	United Kingdom (2015)	449	Single-center, retrospective, 1993–2011	Median = 74 months (range < 1–221)	• NMD = 56% • Lung/airway disease = 20% • Congenital Sd = 14%	NIV only
Weiss et al. (20)	Austria (2016)	143	National, cross-sectional, 2013	— —	• NMD = 44% • Other neurological = 28% • OSA =8.5% • Chest/spine = 8.5 • Lung = 5%	34/60% CPAP = 6%
Chau et al. (9)	Hong Kong (2017)	96	Single-center, retrospective, 1997–2015	Mean = 5.2 ± 6 years for IV, 10.3 ± 7.6 years for NIV	• NMD = 50% • CNS = 25% • Airways = 18% • Chronic lung disease = 6%	26/56% CPAP: 17%
Nathan et al. (21)	Malaysia (2017)	70	Single-center, retrospective, 2001–2014	Median = 11 months (range 5–22)	• Lower respiratory = 49% • Upper airways = 9% • Chest/spine = 11.5% • NMD = 10% • Cardiac disease = 8.5% • Spinal cord injury = 7%	14/43% CPAP: 43%
Van der Poel et al. (22)	South Africa (2017)	55	Single-center, retrospective, 1994–2015	Median = 3.5 years (range 0.4–17.6)	• NMD = 60% • Various = 18% • CNS = 9% • Chest wall = 3.5% • Spinal = 3.5% • Cardiac = 3.5%	71/29%
Ikeda et al. (14)	Japan (2018)	123	Single-center, retrospective, 2001–2015	Median = 139 months (range 8–223)	• NMD = 36% • Congenital anomaly = 21% • Metabolic/degenerative disease = 20% • Perinatal disorder = 11%	57/43%

(Continued)

TABLE 1 | Continued

Author	Country	No. of patients	Study type	Age at initiation	Main diagnoses	IV/NIV
Hassani et al. (23)	Iran (2019)	67	Single-center, retrospective, 2013–2015	Mean = 5.2 ± 4.9 years	• Lung/airway disease = 45% • NMD = 31% • Metabolic disease = 13.5% • Others = 10.5%	9/32% CPAP: 49%
Park et al. (24)	Korea (2019)	416	National, cross-sectional, 2016	Median = 6 years (range 2–14)	• NMD = 52% • CNS = 34% • Cardiopulmonary = 14%	49/51%
Leske et al. (15)	Argentina (2020)	244	Single-center, retrospective, 2007–2018	Median = 9.4 years (IQR 3.5–14)	• NMD = 43% • Genetic Sd = 23%	14/86%
Pavone et al. (25)	Italy (2020)	432	Single-center, retrospective, 2000–2017	Median = 6.4 years (IQR 1.2–12.8) for NIV, 2.1 years (IQR 0.8–7.8) for IV	• NMD = 30% • Upper airways = 25% • CNS = 23%	27/73%

IV, invasive ventilation; NIV, non-invasive ventilation; NMD, neuromuscular disease; CNS, central nervous system disease; CPAP, continuous positive airway pressure; §, one patient with negative pressure ventilation.

available, such as neurodevelopment, facial growth, and quality of life (27).

INDICATIONS FOR LONG-TERM NON-INVASIVE VENTILATION

General Considerations

Chronic respiratory failure, defined by the inefficiency of the respiratory system to ensure appropriate blood-gas exchange meeting the metabolic requirements of a subject, can manifest by a decrease in PaO_2 only, or by both an increased $PaCO_2$ and a decreased PaO_2, indicating chronic alveolar hypoventilation. The former can usually be treated with nasal oxygen therapy alone. In the presence of chronic alveolar hypoventilation, long-term mechanical ventilation might be needed, now usually given in the form of LT-NIV.

Diagnosis of chronic alveolar hypoventilation rests on the identification of chronic hypercapnia. Since, as a rule, alveolar hypoventilation manifests first during sleep, chronic hypercapnia was traditionally identified from an arterial or arterialized capillary blood sample taken upon awakening in the morning. Whole-night recording of transcutaneous PCO_2 + oximetry has now largely replaced morning blood sampling (28). Conversely to diurnal hypercapnia ($PaCO_2 > 45$ mmHg), however, there is no consensual definition of nocturnal hypercapnia. Although the American Academy of Sleep Medicine defines hypercapnia as 25% or more of the recording time spent with a $PCO_2 > 50$ mmHg (27), other experts consider this definition overly restrictive (28, 29).

The overall aim of LT-NIV is to increase life expectancy and maximize quality of life by augmenting alveolar ventilation and restoring normocapnia, hence preventing the deleterious consequences of chronic alveolar hypoventilation. This is not always possible, however, for a variety of reasons, such as patient discomfort with LT-NIV, especially with the interface. If normocapnia cannot be achieved, every effort must be made to ensure that home LT-NIV provides for alleviating the clinical symptoms of alveolar hypoventilation (see **Table 2**), discharging the child earlier from the hospital, and preventing complications such as frequent respiratory infections and failure to thrive.

TABLE 2 | Clinical signs of chronic alveolar hypoventilation.

Insomnia, nightmares, and frequent arousals
Nocturnal or early morning headaches
Shortness of breath during activities of daily living
Daytime fatigue, drowsiness and sleepiness, loss of energy
Decrease in intellectual performance
Loss of appetite and weight; impaired swallowing
Recurrent respiratory infections
Signs of cor pulmonale

Today, home mechanical ventilation most often consists in non-invasive positive pressure ventilation during the night, preferentially via a nasal mask. While some patients with excessive non-intentional oral leaks necessitate the use of an oronasal mask for LT-NIV—less often a total face mask—both must be used with great caution due to the risk of lung aspiration during vomiting. This is especially true for infants and small children, as well as for subjects unable to remove their mask because of muscle weakness/paralysis or intellectual disability (30, 31). Nighttime LT-NIV can be insufficient in patients with severe chronic respiratory failure, either permanently or during an acute aggravation (e.g., during respiratory infections). Daytime NIV can then be added to nighttime LT-NIV, either via the mask used at night or via a mouthpiece, depending on the patient's preferences and their capability to use a mouthpiece. The latter has the distinct advantage of allowing the patient to tailor their ventilatory needs to the ventilatory assist and facilitates interactions with relatives.

Consequently, it is usually preferred over a nasal mask for daytime ventilation (32).

Delivery of home LT-NIV necessitates the existence of a home ventilation program, whose characteristics have been described (33, 34). Close collaboration is mandatory between the hospital multidisciplinary team (who initiates LT-NIV and supervises the medical follow-up and complex care of the patient), the personnel from the home-ventilation program (who ensures equipment delivery; sets up, monitors, and adjusts LT-NIV as prescribed by the hospital team; and answers emergency calls 24/7), and the family caregivers. Monitoring LT-NIV has become a crucial component in home-ventilation programs. In addition to regular oximetry and transcutaneous PCO_2 recording, built-in ventilator software allows the monitoring of patient adherence and respiratory variables. Telemonitoring is a growing trend in home-ventilation programs. It is generally well-accepted and viewed as advantageous by both patients and family caregivers, as well as by the personnel from the home ventilation program and the hospital complex-care team. Data on telemonitoring benefits for day-to-day care, mean- to long-term outcome, and cost-effectiveness are, however, very limited, especially in children (33, 35, 36).

TABLE 3 | Potential indications for long-term non-invasive ventilation.

Respiratory pump	Neuromuscular diseases
	Chest wall deformity/kyphoscoliosis
	Spinal cord injury
	Prune-Belly syndrome
Respiratory drive	Congenital central hypoventilation syndrome
	Brain/brainstem injury
	Central nervous system tumors
	Metabolic disorders
Airway	Craniofacial malformations
	Obstructive sleep apnea
	Tracheomalacia
	Bronchomalacia
Pulmonary parenchymal and vascular problems	Chronic lung disease of infancy (bronchopulmonary dysplasia)
	Lung hypoplasia
	Recurrent aspiration syndromes
	Cystic fibrosis
	Congenital heart disease

With permission from (39).

Medical Conditions Treated by Long-Term Non-invasive Ventilation

Chronic respiratory insufficiency can be caused by conditions that affect respiratory-muscle performance (alterations in central respiratory drive or neuromuscular function) and/or impose an excessive respiratory load (airway obstruction, lung disease, or chest-wall restriction) (37, 38). **Table 3** lists the potential indications for long-term non-invasive ventilation (39). Examples of alterations in central respiratory drive are congenital central hypoventilation syndrome (40, 41), ROHHAD (rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) (42, 43) and various brainstem anomalies, such as Chiari type II malformation (44). Cerebral palsy can also lead to central hypoventilation, in addition to upper airway obstruction, spine and chest wall deformity, and/or chronic lung disease (45). Central hypoventilation can also contribute to chronic alveolar hypoventilation in congenital syndromes such as Prader-Willi syndrome (46) or Down syndrome (47). Examples of neuromuscular disorders responsible for chronic respiratory insufficiency in pediatrics include type I and type II spinal muscular atrophy in infants/young children (48), as well as various inherited myopathies, the most common being Duchenne muscular dystrophy in adolescents (49). The use of LT-NIV to manage chronic respiratory insufficiency due to high-level spinal-cord injury has also been reported in a number of patients (50). Congenital or acquired chest-wall deformities, such as severe kyphoscoliosis or spondylothoracic dysplasias, can lead to thoracic insufficiency syndrome and require LT-NIV (49). A number of children with non-surgical, severe upper-airway obstruction insufficiently improved by CPAP can avoid tracheostomy with the use of LT-NIV (27, 51). Chronic lung diseases can also benefit from LT-NIV. These include severe cystic fibrosis in adolescents, in whom LT-NIV has been attempted not only to improve quality of life and prevent deterioration, but also as a bridge to lung transplantation, albeit with mixed evidence (33, 52, 53). LT-NIV has also been utilized for some inherited metabolic disorders, which can variably involve the various components of the respiratory system from the brain to the lungs (54). Conversely, if needed, home ventilation is usually provided via tracheostomy in infants with severe bronchopulmonary dysplasia, most often with pulmonary arterial hypertension (33, 34, 55). And while bronchopulmonary dysplasia is listed as a potential indication, including as a bridge from invasive ventilation to spontaneous ventilation without respiratory support, extensive review of the literature finds very few infants with this diagnosis in reports on home LT-NIV (17, 56, 57). Lastly, morbid obesity associated with upper-airway obstruction, restrictive lung disease, and central hypoventilation (obesity-hypoventilation syndrome) can necessitate LT-NIV (33).

CONTRAINDICATIONS FOR LONG-TERM NON-INVASIVE VENTILATION

While it is commonly stated that there are no absolute contraindications for LT-NIV, not all patients are eligible. The following conditions may preclude the initiation or adherence to LT-NIV and may lead to considering alternative treatments, such as invasive ventilation via tracheostomy, in concert with the family and patient. It must however be underlined that most contraindications can be successfully managed through a close collaboration between a hospital-based LT-NIV expert team and the personnel from the home-ventilation program.

Inability to Protect the Lower Airways and Lack of Cooperation From the Patient and/or Family

Inability to protect the lower airways and lack of cooperation from the patient and/or family are often listed as the most important contraindications.

Inability to Protect the Lower Airways

Inability to protect the lower airways, due to bulbar impairment or weakened muscles of the upper aerodigestive tract, can lead to dysphagia and lung aspiration with potentially severe acute, subacute, or chronic consequences. The risk of aspiration can come from sialorrhea or occur with feeding or vomiting. Sialorrhea can be treated with anticholinergic medications or repeated injections of botulinum toxin A into the salivary glands (58). Surgery of the salivary glands is another option, especially in children with cerebral palsy (59). Aspiration during feeding is usually managed first by appropriate texture modification of food, then by enteral feeding via a gastrostomy. Diurnal non-invasive ventilation can also decrease respiratory rate, allowing more time for post-swallow expiratory apnea, consequently decreasing the risk of aspiration (60). Moreover, recent studies have shown that, conversely to nasal ventilation, mouthpiece ventilation during meals represents a significant advantage for swallowing and can allow safe feeding when alternating mouthpiece insufflation and swallowing, especially with non-solid food. Improved swallowing with mouthpiece ventilation is likely due to an increase in lung volumes, as well as a decrease in respiratory rate (61–63).

Weak Cough

A weak cough impairing the handling of secretions is usually efficiently managed with assisted-cough techniques, which include manually assisted cough ± inspiratory-air stacking or the use of mechanical in/exsufflation (64).

Gastroesophageal Reflux

Gastroesophageal reflux uncontrolled by medications and fundoplication might be considered a contraindication to LT-NIV, especially in children with impaired swallowing. An oronasal mask must not be used in such circumstances (65). The decision to proceed to a trial of LT-NIV with a nasal mask should take into account evidence from human and animal studies showing that positive airway pressure therapy, including NIV, can inhibit gastroesophageal reflux (66, 67).

Lack of Cooperation From the Patient

Lack of cooperation from the patient is frequent in infants and young children, as well as in children with intellectual disability. While hindering initiation and adherence to LT-NIV, it is generally less of a problem in experienced centers (34). Problems with interface and headgear fitting—frequently encountered in infants and young children—can thus be rapidly and efficiently overcome. Customized ventilatory parameters, which significantly relieve symptoms, can be found without undue delay. As well, the fear sometimes expressed by older children and adolescents that LT-NIV might aggravate the disease (e.g., by deconditioning the respiratory muscles in Duchenne muscular dystrophy) can be discussed beforehand, and the lack of perception of the benefits of LT-NIV rapidly recognized and dealt with. In all these circumstances, full cooperation from the family is of the utmost importance for successful LT-NIV. A family's lack of cooperation or inability to understand recommendations can preclude or delay LT-NIV.

Other Relative Contraindications

Anatomic Facial Abnormalities

Anatomic facial abnormalities can at times interfere with interface fitting and lead to considering invasive ventilation via tracheostomy (68).

Presence of Complications Related to the Interface

The presence of complications related to the interface, such as skin ulcerations or mid-face hypoplasia, should no longer be considered contraindications for continuing LT-NIV. Skin ulcerations should be prevented or cured by alternating several masks with different pressure points or by using a cloth mask (69) or a custom-molded mask (70). Mid-face hypoplasia has been shown to complicate nasal-mask respiratory support in a substantial proportion of children—up to 30% (71)—leading to class III malocclusion (72, 73). Beyond an orthodontic consultation at least yearly, which is recommended for all children with LT-NIV, the use of different masks or the preference for either a cloth mask or a custom-molded mask, might prevent the development of mid-face hypoplasia (74). This, however, remains to be proven.

Need for Ventilator Support for More Than 16 h a Day

The need for ventilator support for more than 16 h a day remains a classic indication for invasive ventilation through tracheostomy, especially in small infants. Older patients, who often perceive tracheostomy as a factor decreasing their quality of life, can be ventilated via a nasal mask or a mouthpiece during the day, as a complement to nocturnal nasal-mask ventilation. A mouthpiece is usually the first choice for diurnal ventilation to avoid facial-skin breakdowns and facilitate speaking, eating, swallowing, and coughing (32, 75). Nevertheless, depending on the patient preference or ability to use a mouthpiece, nasal-mask ventilation can also be used around the clock (76, 77). Following reports that diurnal mouthpiece ventilation was associated with longer survival than invasive ventilation (78), many experts now strongly advocate for the use of non-invasive ventilation when both nocturnal and diurnal ventilation are needed.

Long-Term Non-invasive Ventilation in Children During the COVID-19 Pandemic

The global COVID-19 pandemic caused by SARS-CoV-2 has raised several concerns for patients on LT-NIV. First, children with LT-NIV are clinically vulnerable and at increased risk of respiratory failure during any viral respiratory infection.

Hence, they are considered at increased risk for severe COVID-19 infection (79). It still is not clear whether the risk is higher with SARS-CoV-2 than other respiratory viruses, such as influenza viruses (80). Of further importance is the fact that, should the child under LT-NIV have COVID-19, LT-NIV can generate aerosols of viral particles, which represent major risks of contamination for caregivers (81). Guidelines on the care of a patient under LT-NIV at home can be found on a few national society websites. Derived from expert opinions, they include proposals for adapting the ventilator equipment and/or the interface, as well as the advice to deliver LT-NIV in a room isolated from the rest of the house (79, 82–84). This becomes of the utmost importance in cases of suspected or confirmed COVID-19 infection, especially if another vulnerable person is present in the household. In such cases, consideration must be given to delivering LT-NIV away from the home. Delaying the initiation of LT-NIV during the peak of the pandemic is also an option in specific cases. Another aspect of LT-NIV during the COVID-19 pandemic is monitoring home LT-NIV and modifying NIV settings as deemed necessary. Telemonitoring and video consultation are becoming genuine assets in preventing contact between the child's family and the personnel from either the home-ventilation program or the hospital complex-care team. It might be more difficult—even impossible—to obtain a full-night in-hospital polysomnography or even night oximetry + transcutaneous PCO_2 recording at home to confirm that the LT-NIV settings are adequate. Such lack of usual surveillance might jeopardize the quality of LT-NIV provided to new and/or complex patients.

CONCLUSION

Home LT-NIV in children is used increasingly worldwide, including in countries with more challenging socioeconomic conditions. Further developments are foreseen, especially in such countries, and can take advantage, to a certain extent, of programs in place elsewhere. Overall, LT-NIV programs provide marked improvement in terms of decreased mortality and increased quality of life to a number of patients with complex disorders involving chronic respiratory insufficiency. While there are a number of indications for LT-NIV, contraindications are few. Many established and forthcoming national home-ventilation programs must, however, be optimized to allow children from all socioeconomic conditions to get access to LT-NIV when needed. Of further importance is the necessity for NIV equipment companies to engage in better collaboration with clinician experts in pediatric LT-NIV in order to develop further NIV equipment tailored to infants and young children. This includes a greater variety of interfaces (masks and headgears) specifically for infants and children, as well as ventilator algorithms and telemonitoring programs for children of all ages to help monitor the appropriateness of LT-NIV.

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REVIEW
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Ventilators and Ventilatory Modalities

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Non-invasive ventilation is increasingly used in children for acute and chronic respiratory failure. Ventilators available for clinical use have different levels of complexity, and clinicians need to know in detail their characteristics, setting variables, and performances. A wide range of ventilators are currently used in non-invasive ventilation including bi-level ventilators, intermediate ventilators, and critical care ventilators. Simple or advanced continuous positive airway pressure devices are also available. Differences between ventilators may have implications on the development of asynchronies and air leaks and may be associated with discomfort and poor patient tolerance. Although pressure-targeted (controlled) mode is preferable in children because of barotrauma concerns, volume-targeted (controlled) ventilators are also available. Pressure support ventilation represents the most used non-invasive ventilation mode, as it is more physiological. The newest ventilators allow the clinicians to use the hybrid modes that combine the advantages of volume- and pressure-targeted (controlled) ventilation while limiting their drawbacks. The use of in-built software may help clinicians to optimize the ventilator setting as well as to objectively monitor patient adherence to the treatment. The present review aims to help the clinician with the choice of the ventilator and its ventilation modalities to ensure a successful non-invasive ventilation program.

Keywords: ventilators, non-invasive ventilation, pressure support ventilation, pressure control ventilation, hybrid modes

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INTRODUCTION

Non-invasive ventilation (NIV) is increasingly used in children for acute and chronic respiratory failure (1, 2).

Ventilators available for clinical use have different levels of complexity and clinicians need to know their characteristics, setting variables, and performances (3, 4).

Differences between ventilators can have implications on air leaks and patient–ventilator interaction, causing asynchronies that may lead to poor NIV tolerance (5).

If the clinician fails to optimize the setting to respond effectively to the patient's requests, there is a greater probability of NIV failure. For these reasons, the choice of the ventilator and the clinician proficiency are crucial steps to improve the chance of a successful NIV program (3–5).

This review is part of the research topic "Pediatric Long-Term Non-Invasive Ventilation," indications and modes of NIV in children affected by chronic respiratory failure will be extensively discussed in other articles that are part of this research topic.

TYPES OF VENTILATOR

There is no consensus about the classification of ventilators; however, they can be categorized as bi-level ventilators, intermediate ventilators, and critical care ventilators (3, 4).

For proper functioning, all ventilators require electricity. This can be supplied as external alternating current or via an internal direct current battery.

Usually, the gas source can be a piston, micro-piston, or more recently a turbine. Fast turbines (also known as dynamic blower systems), or turbines rotating at constant speed (also known as constant-revolution blower systems) are highly efficient and are used in the latest generation of turbine-driven ventilators (6).

Most ventilators only possess a low-pressure oxygen inlet. With this configuration, oxygen delivery is not constant and very high FiO_2 levels cannot be achieved. Some ventilators may work with oxygen at high pressure and may deliver a constant preset oxygen tension, independent of the minute volume ventilation (7).

NIV in children can be performed using volume-targeted or pressure-targeted (controlled) ventilators, based on the *control* variable with which the ventilator delivers the inspiration (4).

A ventilator produces a volume-targeted or a pressure-targeted ventilation if, respectively, the wave profile of the flow (in volume-controlled mode) or pressure (in pressure-controlled mode) delivered during inspiration does not vary with changes in the mechanics of respiratory system in terms of compliance and resistance (4).

In volume-targeted ventilation, the mechanical breath generates a preset volume during a given time. In pressure-targeted ventilation, the mechanical breath generates a preset pressure during a given time (4). Some ventilators are able to combine volume and pressure, so that hybrid modes can be performed (8).

In NIV, pressure-targeted (controlled) mode is the most often used due to its ability to compensate for leaks and to generate constant pressures when compared with volume-targeted ventilation (8, 9).

This article will focus mainly on positive pressure ventilation modes in the long-term setting. There will be a section dedicated to hybrid modes and a summary on volume-targeted ventilation. Critical care ventilators used in the acute clinical setting will not be described.

Bi-Level Ventilators

Bi-level ventilators are the most common devices used to perform NIV. These ventilators are configured with a single-limbed vented circuit and designed to operate in the presence of leaks (8).

The leaks are necessary to flush the circuit of exhaled air gases and carbon dioxide through a leak port. These ports can be located either in the circuit (i.e., whisper swivel, Philips Respironics, Murrysville, PA, USA) very close to the patient interface or in the interface (i.e., so-called vented masks). The risk of rebreathing is reduced by using a baseline expiratory positive pressure. In some bi-level ventilators, expiratory pressure cannot be set below 3 or 4 cmH_2O to assure that the circuit is adequately flushed (4, 8, 9).

The newest bi-level ventilators allow the clinician to indicate the interface used during NIV (9). This feature allows the device to better identify intentional and unintentional leaks so that the flow can be adjusted to guarantee desired performances. Estimates of tidal volume and leaks are determined through algorithms specific to the devices (8). Bi-level ventilators work properly in the presence of certain amount of leaks that may vary between devices. Leaks that impair proper trigger or cycle functioning must be considered as unacceptable (9).

The newest bi-level ventilators provide several modes, displays, alarms, batteries, and internal oxygen blenders (3, 4, 6–8).

Intermediate Ventilators

Intermediate ventilators may have single- or dual-limbed circuit configurations. Single-limb configuration has either an active exhalation valve usually close to the patient airway (non-vented configuration) or a passive leak (vented configuration). Current intermediate ventilators allow various pressure- or volume-targeted modes. Some devices may also be equipped with hybrid modes like average volume-assured pressure support and intelligent volume-assured pressure support (8).

Like bi-level devices, intermediate ventilators possess several modes, displays, graphics, alarms, batteries, and internal oxygen blenders (3, 4, 6–8).

RESPIRATORY CIRCUITS

Ventilators deliver pressure to the airway by a respiratory circuit. The proximal part of the respiratory circuit is connected to the ventilator, and the distal part is connected to the patient through a non-invasive interface.

As briefly mentioned above, three main types of circuit are available.

In the single-limb respiratory circuit, inspiration and expiration occur through the same limb, and this would potentially lead to carbon dioxide rebreathing (10). In order to avoid this rebreathing, two different systems are available:

1) The *non-vented* respiratory circuit is a single circuit equipped with a non-rebreathing expiratory valve. This valve (e.g., a mushroom valve driven by ventilator pressure) has an on–off function and allows complete elimination of carbon dioxide. Usually, this circuit provides only inspiratory tidal volume measurement (11).
2) The *vented* respiratory circuit or intentional leak respiratory circuit is a single respiratory circuit without a "true" non-rebreathing active valve. In this configuration, carbon dioxide is vented out through passive exhalation ports (i.e., whisper swivel, Philips Respironics, Murrysville, PA, USA). The efficacy of this exhalation may be affected by several factors such as the level of expiratory positive airway pressure, the combined amount of intentional and unintentional leaks, and the supplemental oxygen delivered into the non-invasive interface. In this configuration, inspiratory or expiratory tidal volumes are indirectly calculated by an algorithm.

The double-limb respiratory circuit includes an inspiratory and expiratory limb. The proximal parts of the respiratory circuits are connected, respectively, to the inspiratory and expiratory ports of the ventilator where inspiratory and expiratory valves are positioned. The distal parts of the respiratory circuits are connected to the Y-piece ending in the patient interface (10). This circuit configuration allows one to measure inspiratory and expiratory tidal volume.

NIV TERMINOLOGY

Terminology associated with NIV modes may vary between bi-level, intermediate, and critical care ventilators, and this may generate confusion. On devices designed primarily for NIV (i.e., bi-level ventilators), the pressure setting is indicated as inspiratory positive airway pressure (IPAP) during inspiration and as expiratory positive airway pressure (EPAP) during expiration. On other devices, including critical care ventilators, during inspiration, the effective pressure generated is the sum of the inspiratory assistance added to the preset positive end expiratory pressure (PEEP) (4, 9).

In the context of the delivery of a positive pressure breath, several variables need to be defined. The *trigger* defines the onset of inspiration criteria, the *limit* defines the inspiratory limit that cannot be overcome during inspiration, the *cycling* defines the transition from inspiration to expiration criteria (3), and the *control* defines whether a breath is volume or pressure controlled.

A mechanical breath can be *triggered* by pressure; volume; a combination of pressure, flow, and volume; waveform algorithms; or time (3, 4, 9). Pressure and flow triggering, respectively, allows detection of a pressure drop or a flow modification within the circuit determined by the patient's inspiratory effort. Newer devices improve patient–ventilator synchrony trough algorithm that combines volume, pressure triggers, and a flow waveform algorithm. Many ventilators enable the clinician to set the triggers' threshold *sensitivity*.

The main goals of a performing inspiratory trigger are the reduction of both the intensity of the muscular effort and the delay between patient's inspiration onset and starting a ventilator delivered breath.

Limit variables are the minimal or maximal values manually adjustable for a mechanical breath according to the set options available among the device features (i.e., minimum inspiratory time, T_{min}, and maximum inspiratory time, T_{max}, in a flow cycled breath).

A mechanical breath can be *cycled* by pressure, time, volume, or flow (3). A breath is defined as time-cycled when it is terminated after a given preset inspiratory time. A breath is defined as flow-cycled when it is terminated after a given inspiratory flow threshold decay (3, 4, 9). Many ventilators allow the clinician to set the *sensitivity* of the threshold of flow termination criteria. This threshold is usually expressed in terms of percentage of peak inspiratory flow or labeled as number.

VENTILATION MODES

Ventilation should be considered as a double compartment respiratory model, where expiratory pressure will favor the upper compartment (upper airway) patency needed to allow the delivery of pressure support to the lower compartment (lower airways) (12).

Non-invasive intermittent positive pressure (NPPV) ventilation differs from continuous positive airway pressure (CPAP) because it provides two different levels of pressure. During NIV, pressure increases during the inspiratory phase of the breath and returns to an elevated baseline during expiratory phase. The pressure increases during the inspiratory phase, augments tidal volume, improves gas exchanges, and unloads respiratory muscles (3, 4, 9).

Continuous Positive Airway Pressure

CPAP is a spontaneous modality in which the work of breathing is completely generated by the patient. Since CPAP does not provide pressure assist during inspiration, it should not be considered a "true" ventilation mode (4). CPAP is usually described in the context of NIV because it shares the circuits, interfaces, and sometimes the same ventilators.

CPAP is based on the delivery of fixed preset pressure to the airways for the entire respiratory cycle (3, 4, 9, 12). On the upper airways, working as mechanical stent, CPAP increases their cross-sectional area and keeps the airway open by elevating the intraluminal pressure above the transmural critical pressure that determines the collapse. On the lower airways, releasing a continuous additive flow, CPAP may prevent alveolar collapse, favors the alveolar recruitment, and increases the functional residual capacity.

Through these mechanisms, CPAP counteracts the obstruction of the upper airways, may prevent atelectasis, improves oxygenation, and downloads the inspiratory muscles, reducing the work of breathing. Moreover, CPAP may reduce afterload and increase cardiac output by lowering left ventricular transmural pressure (3, 4, 9, 12). CPAP may also stabilize chest wall distortion.

Auto-titrating CPAP is an advanced mode during which the delivery of positive airway pressure is adjusted automatically between a range of values set by the clinician, according to either the analysis of the flow curve or airway resistance [forced oscillation technique (FOT)] performed by the device's software. By using auto-titrating CPAP devices, pressures may vary based on the patient's needs at various time of the night (i.e., higher pressure during REM sleep). This could allow the patient to receive, on average, lower pressures during the night and experience fewer side effects related to higher pressures (13).

In some devices, more advanced CPAP modes are also available. These modes are mainly characterized by a moderate decrease in airway pressure at the beginning of expiration, or a variable increase in airway pressure during inspiration (14).

Manufacturers recommend a minimum weight (10–30 kg), for use of the auto-titrating and advanced CPAP modes.

Volume-Targeted (Controlled) Ventilation

In volume-targeted (controlled) ventilation, as previously mentioned, the ventilator is set to deliver a fixed volume (independent variable) during a given time span. This fixed volume will be delivered whatever pressure (dependent variable) is necessary to reach the target, regardless of the patient contribution to ventilation. The effective pressure released to the airways will depend on the interaction between ventilator settings, spontaneous patient inspiratory efforts, and mechanics of the respiratory system. Further inspiratory effort does not change delivered volume or flow (9, 15, 16).

The advantage of this mode is the strict delivery of the preset volume in the absence of leaks and regardless of the compliance and resistance of the respiratory system. The disadvantages of this mode are essentially two. The first is the delivery of a fixed volume that occurs independently of the varying needs of the patients. The second is that, with increasing leaks, there is no proportional compensatory increase in flow rate, which results in lower effective pressure and reduced volume (9, 15, 16).

Pressure-Targeted (Controlled) Ventilation

In pressure-targeted (controlled) ventilation mode, the ventilator delivers airflow by generating a preset positive pressure (independent variable) in the airways for a given time (9, 15). Flow is the dependent variable. Thus, the volume delivered in the airways will not be fixed and will result from the interaction between the patient inspiratory effort, the preset pressure, the inspiratory time, and the mechanics of the respiratory system (15).

Advantages of pressure-targeted (controlled) ventilation include the ability to compensate for mild to moderate leaks and improvements in synchronization since flow can vary breath by breath (3, 4, 9, 15) A limitation of pressure-targeted (controlled) ventilation mode is that tidal volume cannot be guaranteed, and this may potentially lead to insufficient ventilation (9, 15). Bi-level positive airway pressure (bi-level) provides respiratory support at two different levels (4, 9, 15, 16). Bi-level ventilation allows, therefore, the clinician to set independently an expiratory and an inspiratory positive airway pressure.

Similarly to CPAP, adding an expiratory positive airway pressure helps keep the upper airways open, and through alveolar recruitment, it reduces the risk of atelectasis and favors the increase of functional residual capacity.

Moreover, in a single limb circuit with a passive exhalation port or a vented interface, expiratory positive airway pressure would prevent the re-breathing of carbon dioxide (10, 11).

The tidal volume will result from the difference between inspiratory and expiratory pressures within certain limits, the flow resistance of the respiratory circuit, any airflow limitations, and the mechanics of the respiratory system (4, 15).

Based on the patient–ventilator interaction, bi-level PAP can be delivered in PSV mode [either in spontaneous (S) or spontaneous timed (ST) mode], or in pressure-controlled ventilation (PCV) mode. The devices may also include a timed (T) or control mode, rarely used because it does not allow for patient synchrony.

PSV Mode

PSV is a pressure-controlled flow-cycled mode. In the *spontaneous* (*S*) mode, in bi-level ventilators, inspiration starts when the patient triggers the ventilator. The inspiratory pressure is maintained as long as a minimum preset inspiratory flow is present. The switch from inspiration to expiration (cycling) occurs when inspiratory flow achieves a preset percentage of peak inspiratory flow. Therefore, in this mode, the patient controls the onset (triggering) and end (cycling) of inspiration, the ventilator supports the respiratory act, and again the patient determines the respiratory rate and pattern (4, 17).

Based on the ventilator used, in spontaneous mode, the clinician can select a target inspiratory positive pressure, trigger sensitivity, and the threshold of peak flow for cycling to expiration. Usually, this threshold is set at 25% of inspiratory peak flow, but most of the available ventilators allow the setting of a wide range of threshold (i.e., 5–80%) (11). Some simpler ventilators allow the clinicians to set only the inspiratory positive pressure (15, 17).

In the *spontaneous/timed* (*ST*) mode, a combination of spontaneous supported flow cycled breaths and mandatory mechanical acts is allowed.

If the patient's spontaneous respiratory rate is lower than the backup respiratory rate, mechanical breaths are triggered, supported, and cycled by the ventilator (4, 17).

During patient-triggered breath, the ventilator cycles in expiration when it senses a drop in inspiratory flow rate below a preset threshold. During device-triggered breath, the ventilator cycles in expiration at a preset time (17).

Based on devices, in this mode, the clinician determines inspiratory and expiratory pressures, backup respiratory rate, and rise (pressurization) time (16). Some devices allow the clinician to dial an inspiratory time, while others allow to dial a range from a minimum (T_{min}) to a maximum inspiratory time (T_{max}) (12).

Bi-level ventilators adopt the terminology IPAP for inspiratory pressure and EPAP for expiratory pressure. While PSV works above a given PEEP level, in bi-level ventilators, if EPAP needs to be increased, the IPAP should be increased as well to keep the same level of inspiratory support. This adjustment maintains the difference between inspiratory and expiratory pressures (4).

A flow cycled breath allows to preserve the patient's spontaneous breathing and to reduce excessive work of breathing (4, 9, 12, 17). PSV is advisable in any condition in which the patient's spontaneous breathing can sustain the proper minute ventilation. On the contrary, this mode is not recommended in patients with significant impairment of the ventilatory drive, with severe depression of consciousness or severe deterioration of muscle pump efficiency (18).

PCV Mode

PCV is a pressure-controlled time-cycled mode. In the *assist* (*A*) mode, inspiration starts when the patient triggers the ventilator. The inspiratory pressure lasts for a preset time (16). Cycling from inspiration to expiration occurs after a given set time (15, 17). Therefore, the patient controls the beginning (triggering) of inspiration, but the inspiratory pressure level, inspiratory

time, and cycling to expiration are provided mechanically by the ventilator. In assist mode, the respiratory rate will be determined by the patient, but the respiratory pattern will be determined by the ventilator.

In the *control* (*C*) mode, the ventilator controls the beginning of inspiration (time triggering), the end of inspiration (cycling), and the respiratory rate (17). In this mode, the ventilator performs the entire work of breathing. Some ventilators call this Timed (T) mode (17).

When a backup respiratory rate is applied, this mode is defined as pressure assist/control (AC-PCV) mode (4, 9, 17). In this last mode, a combination of assisted spontaneous breathing and controlled acts is allowed. If the patient's spontaneous respiratory rate is lower than the preset ventilator backup respiratory rate, the system switches from assist (patient-triggered breaths) to control (device-triggered breaths) mode. Thus, triggering by the patient is allowed, but the ventilator delivers a breath with the same inspiratory time of the mandatory breath.

Based on devices, in AC-PCV mode, the clinician selects inspiratory and expiratory pressures, inspiratory: expiratory (I:E) ratio, or inspiratory time, inspiratory trigger sensitivity, and rise time (17). However, inspiratory time in patients with a respiratory activity should be set according to the actual patient's rate. For this reason, many clinicians prefer the ST mode.

This mode is advisable in severely ill patients with significant impairment of the ventilatory drive or of the muscle pump efficiency (18).

HYBRID MODES

As previously briefly discussed, some new ventilators provide hybrid modes. Hybrid modes, known as volume-targeted (adaptive) pressure ventilation, use intelligent algorithms to automatically adjust the setting to achieve predefined targets (9, 17). Hybrid modes combine the advantages of conventional volume and pressure-targeted (controlled) ventilation (8, 17) and can be used in either pressure support or control mode.

Ventilators may have different algorithms and setup variables, and this explains differences in their response (8, 9, 15, 17). Some ventilators can adjust a target volume within each cycle, while others can progressively adjust the pressure level during several cycles (8, 17).

Ventilators can provide volume-targeted (adaptive) pressure ventilation with all the respiratory circuit configuration previously described (9, 16).

Volume-targeted (adaptive) pressure ventilation is, essentially, an adaptive dual-targeting mode that should permit the ventilator to properly compensate for possible changes in respiratory mechanics ensuring a constant and effective ventilation (8). According to the different algorithms, adjustments in inspiratory pressure (first target) take place to deliver the predetermined target volume (second target) (8).

The control variable is inspiratory pressure, constrained between a range of values (minimum and maximum) set by the clinician. Inspiration starts as a pressure-targeted (controlled) mode. Once the devices have measured or estimated the delivered volume, it determines whether to remain unchanged or to modify, before cycling to expiration, the inspiratory pressure level to achieve the dependent variable, which is the preset target volume (8, 16, 18).

For a given patient, the minimum inspiratory support should be set to a safe level of tidal volume. The maximum pressure support should be set to allow the ventilator to increase inspiratory pressures and compensate for drops in target volume due to air leaks or reduced inspiratory effort (8).

In addition to the range of inspiratory pressures, the settings include the titration of the expiratory positive airway pressure with the aim to maintain airway patency. The expiratory positive airway pressure can be fixed or, in some ventilators, automatically adjusted between a range of pressures (minimum and maximum) set by the clinician. To achieve this goal, most new ventilators use a combination of snore and flow detection (8, 12).

Moreover, some new ventilators allow setting a variable backup respiratory rate. By automatically adjusting inspiratory and expiratory pressures and backup respiratory rate in a preset range to achieve a target ventilation, these ventilators are able to provide a fully automatic mode (8, 12, 17).

Some ventilators include a learning mode in which the device tends to reproduce the patient's breathing pattern and determines target ventilation (8, 9). However, the use of this mode is not standard practice.

Average Volume-Assured Pressure Support

Average volume-assured pressure support is a form of volume-targeted (adaptive) pressure control ventilation in which the level of pressure support adapts to deliver an average tidal volume (14). In this mode, the target is the expiratory tidal volume and the tidal volume produced by the patient is averaged over 1 min. Then, the algorithm changes the inspiratory pressure according to the speed rate set by the clinicians (from $\pm$ 1 up to 5 cm H_2O per minute) for the subsequent breaths until the target tidal volume is reached (12).

The target tidal volume can be determined through various methods including those based on ideal body weight, measurement of carbon dioxide level during wakefulness or sleep, or by determining a "comfortable" level for that patient and then setting the goal 110% higher.

Some devices possess the auto-EPAP (AE) algorithm. In the average volume-assured pressure support-AE devices, the technique of the forced oscillations is used to measure the airway resistance. In the presence of obstructed airways, the flow oscillations of the forced oscillation technique sinusoidal signal will be smaller than a baseline with patent airways and the EPAP will increase, within preset limits, after the analysis of several breaths (12).

In average volume-assured pressure support mode, backup respiratory rate can be fixed or autoset (two breaths less than the average rate of the most recent six resting spontaneous breaths).

Usually, in this mode, the clinician sets tidal volume, minimum/maximum inspiratory pressures, expiratory pressure (or minimum/maximum expiratory pressure in the case of the auto-EPAP), backup respiratory rate, and rise time (14).

Accurate monitoring of the actual tidal volume is crucial for proper algorithm compensation. Expiratory tidal volume can be measured in the presence of a pneumotacograph placed on the expiratory port of the ventilator as for some turbine-driven ventilators configured with a double-limbed circuits. In case of leaks, this configuration may underestimate the real tidal volume and overcalculate the delivered volume (19). Expiratory tidal volume can be estimated in the absence of a pneumotacograph as for single limb intentional-leak circuit configuration. Some ventilators, even during constant leakage, are able to accurately estimate expiratory tidal volume, rebuilding the patient's flow pattern considering the ventilator's turbine speed, the detection of leaks (either intentional or unintentional), and the onset and the end of inspiration (19). In this way, the ventilators calculate a baseline breathing pattern (patient's zero flow) to obtain an estimated expiratory tidal volume equal to the inspiratory tidal volume (8, 20).

This mode is increasingly used for the management of children poorly responsive to the previously described modes. Successful experiences have been described in infants, children, and adolescents with neuromuscular disease (congenital myopathy) (21), disorders of ventilatory drive (congenital central hypoventilation syndrome) (22–24), and morbid obesity (25).

Intelligent Volume-Assured Pressure Support

Intelligent Volume-Assured Pressure Support is designed to maintain a predefined target alveolar minute ventilation. This target is achieved by monitoring the delivered ventilation, adjusting the inspiratory pressures and automatically activating an intelligent backup respiratory rate (8, 9, 12). The intelligent volume-assured pressure support is indicated for patients weighing 30 kg or more.

The pressure support is continuously adjusted breath by breath in order to maintain target alveolar ventilation. The pressure support adjustment range is limited by the values of minimum and maximum pressure. The breath-by-breath changes in pressure support depend on the respiratory rate and the difference between actual and target alveolar ventilation (12).

The alveolar ventilation value is obtained by subtracting the estimated dead space from a minute ventilation target. Either dead space or minute ventilation can be estimated by indicating the patient's height and respiratory rate, or by selecting disease specific preset values (for normal, obstructive, restrictive lung mechanics, and obesity hypoventilation) available within the device features. The clinician can manually increase or decrease the programmed target alveolar ventilation (12). The target alveolar ventilation can also be determined by measuring of carbon dioxide level during wakefulness or sleep, or assessing the patient comfort at a particular setting (8, 9, 12).

The intelligent backup rate self-regulates the respiratory rate between two limits. The upper limit for intelligent backup rate is the patient's target respiratory rate and should be set to match the patient's average spontaneous rate. The lower limit for intelligent backup rate is two-thirds of the patient's target respiratory rate. During spontaneous breathing, the intelligent backup rate adjusts to two-thirds of the patient's target respiratory rate in order to let the patient spontaneously activate the inspiratory trigger. When the spontaneous inspiratory trigger ceases (e.g., at the beginning of an apnea/hypopnea), the intelligent backup rate intervenes by delivering the patient's target respiratory rate. A single breath with spontaneous inspiratory trigger returns the intelligent backup rate to two-thirds of the patient's target rate (15).

The cycling variables can be either inspiratory time or the percentage of inspiratory flow decay.

The expiratory positive airway pressure can be fixed (manually set) or automatically adjusted within a range of pressure values (minimum and maximum) set by the clinician (8).

In addition, intelligent volume-assured pressure support allows a "learning" mode, which is a period of time (usually 20 min during spontaneous breathing under 4 cmH_2O) during which the device software, by measuring the patient's respiratory rate and tidal volume, computes a target minute ventilation (12, 15).

There is currently very little data in the literature on the use of this ventilation mode in children. A study performed on children with congenital central hypoventilation syndrome reports that the use of the intelligent volume-assured pressure support was associated with a reduction in the maximum transcutaneous carbon-dioxide level during NREM sleep as compared to traditional ST mode (26).

ASYNCHRONIES

The superimposition of mechanical breaths on spontaneous breathing children remains a challenge for a number of reasons including the age-related small tidal volumes and the high respiratory rates (5, 27). These factors combined with the air leaks may lead to patient–ventilator asynchrony (27).

A patient–ventilator asynchrony occurs when one or more phases of breath delivered by the ventilator do not match the phases of breath of the patient (5, 27, 28).

There are various classifications of the patient–ventilator asynchrony and there is no definitive consensus (5, 27–29). They can be classified as asynchronies occurring during the inspiratory period, during the transition from inspiration to expiration, and during the expiratory period.

Below are reported the most frequent patient–ventilator asynchronies. For further details, see specific articles on this topic (5, 27, 28).

Ineffective triggering (also called *missed triggering* or *wasted effort*) occurs when an inspiratory muscle effort is not followed by a ventilator mechanical breath. This type of asynchrony can occurs when the patient initiates a breath that does not reach the ventilator's trigger threshold (5, 27, 28).

There are some situations (called *trigger delay*) where there is a relevant delay between the time of activation of the respiratory muscle and the time of activation of the trigger (5, 27, 28).

Double triggering occurs when a sustained inspiratory effort persists beyond the inspiratory time of the ventilator, the cessation of inspiratory flow, or the onset of a mechanical

expiration. This persistent inspiratory effort consequently triggers a second ventilator breath (5, 27, 28).

Reverse triggering occurs when ventilator insufflation triggers diaphragmatic muscle contractions by activating the patient's respiratory drive in response to a passive insufflation of the lungs (5, 27, 28).

Other asynchronies (called *cycle* or *termination asynchrony*) occur when there is a mismatch between the patient's neural inspiratory time and the ventilator's inspiratory time.

Premature or *short cycling* occurs when the neural inspiratory time is longer than the ventilator's inspiratory time. The patient's inspiratory effort continues, but the ventilator ends flow delivery. The premature cycling occurs at the beginning of expiratory phase (5, 27, 28).

Auto-triggering also known as *auto-cycling* occurs when a cycle delivered by the ventilator is not triggered by the patient (5, 27, 28).

Prolonged or *delayed cycling* occurs when the ventilator mechanical insufflation persists after the end of the neural inspiration or even during an active expiration (5, 27, 28).

BUILT-IN SOFTWARE

Advances in technology resulted in new sophisticated ventilators equipped with built-in software, which may supply information about trends of patients on home ventilation. Built-in software data are potentially useful for the clinician to understand possible causes of not adequate ventilation (30). Companies are investing on software to provide data to clinicians to easily assess the quality of home ventilation. Data can be downloaded from a USB drive or device SD card or using wireless or Bluetooth communication. Data acquired from ventilators are mainly about adherence, leaks, and efficacy of therapy. Adherence data, expressed differently by different software, objectively establish non-use of ventilator and eventual causes of failure of ventilation. Moreover, air leaks could affect adherence creating discomfort, and this information is useful to eventually change settings and interface, if required. Furthermore, some modern ventilators provide data about efficacy of ventilation calculating the Apnea–Hypopnea Index, ventilation parameters, and cycling information during ventilator use (31, 32). Finally, data reports can include a section with detailed data analysis in which clinicians can analyze cycle by cycle the whole course of ventilation (32).

Although built-in software data are a useful tool for the clinician to understand home ventilation trends, there are several limitations on their routine use, such as lack of standardization of built-in software interpretation. In addition, there are no commercially available pediatric specific built-in software or validated data. Hence, currently, those data are available to understand trends of ventilation, but they cannot be considered as diagnostic tools.

As stated above, there are devices that provide only manual data reports (from a USB drive or device SD card) and others that offer in addition wireless/Bluetooth communication and, in few cases, smartphone-friendly data reports. Remote communication enables transmission of data using an internet connection (30). Thereby, clinicians can have easy access to ventilator data and can verify more frequently adherence, leaks, and efficacy of ventilation without the presence of the patient. A current limitation of telemonitoring systems is that data are not transmitted in real time and close follow-up is not possible. Another important limitation, shared by manual and remote data reports, is that, at this moment, information format provided vary greatly between different manufacturers, determining a non-homogeneous interpretation of data supplied to clinicians (29–31).

CONCLUSIONS

A wide range of ventilators are currently available for clinical use. Bi-level and intermediate ventilators are mostly used for NIV. Simple or advanced CPAP (i.e., auto-titrating CPAP) devices are also available.

Volume-targeted and pressure-targeted (controlled) modes are available. Pressure-targeted (controlled) modes are preferable and flow-cycled modes such as PSV represent the most used NIV mode, as it is the most physiological mode.

The newest ventilators allow clinicians to use the hybrid modes, which combine the advantages of volume- and pressure-targeted (controlled) ventilation while limiting their drawbacks.

The use of in-built software may help clinicians to optimize the ventilator setting as well as check patient adherence to the treatment objectively.

AUTHOR CONTRIBUTIONS

MP contributed to the research and critical evaluation of the available literature and wrote the first draft of the paper. EV and AO contributed to the research and critical evaluation of the available literature and to writing sections of the paper. SC contributed to the research and critical evaluation of the available literature and paper. RC contributed to writing the first draft of the paper. All authors read and approved the final manuscript.

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Interfaces, Circuits and Humidifiers

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Long-term non-invasive ventilation (LTNIV) has been increasingly used in children to manage chronic respiratory failure and airway obstruction. Interfaces are of paramount importance for non-invasive ventilation (NIV) effectiveness and patient compliance. However, historically, the choice of pediatric mask has been limited by the scarce availability of commercial interfaces. In recent years, an increasing number of different masks have been commercialized for children, allowing to increase the number of patients who could benefit from LTNIV. Factors such as the age of the child, disease, craniofacial conformation, type of ventilator and mode of ventilation, and children's and family's preferences should be taken into account when selecting the appropriate mask. Adverse events such as skin lesions, facial growth impairment, and leaks must be prevented and promptly corrected. Humidification is a controversial issue on NIV, but it may be useful in certain circumstances. Regular cleaning and disinfection of interfaces and equipment must be addressed. During follow-up, educational programs, close supervision, and continuous support to children and families are crucial to the success of LTNIV therapy.

Keywords: non-invasive ventilation, pediatrics, interfaces, circuits, humidification, adverse events

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INTRODUCTION

Long-term non-invasive ventilation (LTNIV) has been increasingly prescribed for the management of respiratory complications in children with a wide range of clinical conditions like obstructive, chest wall, neuromuscular, central nervous system, and chronic lung disorders (1–3).

Opposite to invasive ventilation, non-invasive ventilation (NIV) provides respiratory support through the use of a mask, thus avoiding tracheal intubation or tracheostomy. Interface choice is of paramount importance when initiating LTNIV, since the presence of leaks or discomfort may affect the efficacy of LTNIV and patients' adherence to treatment. Over the last years, an increasing number of industrial interfaces have become available for infants and children, with adapted mask and headgear design and ergonomics, and the use of more appropriate materials (4, 5).

When starting any children on LTNIV, different types and sizes of masks should be available to allow the selection of the most appropriate interface. Studies comparing interfaces' performance and comfort are scarce in adults and even more in children, with most of the published studies reporting bench data. Nevertheless, the choice of the interface is also associated with local commercial availability, respiratory care center's experience, and child and family preferences.

Finally, few reviews addressed circuits' and humidifiers' characteristics and indications. The objective of this review is to be a practical and comprehensive reference to the available masks, circuits, and humidification options in LTNIV.

INTERFACES

Interfaces influence compliance, comfort, synchrony, and ventilators' performance (6, 7). An ideal interface is lightweight, is stable, is non-traumatic, has minimal dead space, is durable, has low resistance to airflow, is available in several sizes, is easy to clean and disinfect, is connectable with any ventilator, is easy to take off in order to avoid aspiration if the ventilator crashes or the patient vomits, and is affordable (8, 9).

Interfaces may be vented, if they have holes to guarantee intentional leaks when a single-limb circuit is used. In this case, expiration occurs through the mask, and a minimal expiratory pressure is required to ensure CO_2 removal from the circuit. Non-vented interfaces, without intentional leak, may be used with double-limb circuits or with a single-limb circuit with an exhalation valve (4). In this case, expiration occurs through the expiratory limb of the circuit or through the exhalation valve, and no minimal expiratory pressure is required.

Interfaces can cover the nose (nasal mask), the nose and the mouth (oronasal mask), the face (total face mask), and in certain particular situations, the mouth only (mouthpiece). Total facial masks, which covers the nose, mouth, and eyes, may be used in particular conditions such as complex craniofacial malformations but are rarely prescribed to home ventilation because of the increased risk of aspiration with emesis, in particular in younger children (10). Nasal pillows (or prongs or cannulas) are minimal contact interfaces, available for children older than 5–7 years. **Table 1** summarizes the characteristics, advantages, and disadvantages of different masks.

Nasal masks are the most used interfaces in both pediatric and adult patients (3, 5, 11). The risk of aspiration is lower, because the mouth is not covered by the mask. Mouth leaks may be avoided by using a pacifier in infants or chin straps in older children (12). Speaking is possible, while eating and drinking should be carefully balanced against the risk of aspiration, especially with bilevel ventilation.

Oronasal masks may be indicated in children who do not tolerate nasal masks or who have important mouth leaks, but limited availability of commercial masks restricts their use to older children (5). The use of oronasal masks limits speech and oral feeding capacity, and there is an increased risk of aspiration if children vomit or in case of ventilator failure. Moreover, in adults with obstructive sleep apnea, the use of oronasal interfaces may worsen upper airway obstruction, thus leading to the need of higher pressures (13).

Nasal pillows or prongs are inserted into the nostrils, and the pressure generated by the continuous positive airway pressure (CPAP) device helps to seal the soft material against the nose inner walls (14). Like nasal masks, they allow the child to eat and speak and have reduced risk of suffocation by vomiting or ventilator failure. Pediatric sizes are not commercially available, so only older children and adolescents are candidates for this type of interface (15). In older children, a trend for better treatment adherence was found for this kind of interface, when compared with nasal mask (16).

Mouthpiece is indicated in patients who need daytime ventilation, mostly neuromuscular patients (17). The patient receives respiratory support through a mouthpiece supported by a flexible arm kept near his/her lips. The patients must be cooperative and have sufficient muscular strength to seal their lips around the mouthpiece (18). Respiratory support is triggered when the patients places their lips in the mouthpiece, creating a small inspiratory pressure or a sip. Some ventilators have a mouthpiece dedicated mode and a very sensitive trigger, which allows the patient to demand respiratory support with minimal effort (19). Angled mouthpiece, the most frequently of 15 or 22 mm, is most commonly used, as it is easier for the patient to grasp (20).

Mouthpiece interface allows the patient to eat and speak and has no risk of skin breakdown (19). Patients on this mode of ventilation can independently perform an air stacking maneuver, which increases patient's peak cough flow and improves airway secretions drainage (20). Mouthpiece ventilation is used during wakefulness, but there are few reports describing the use during sleep with a lip-seal apparatus that keeps the interface secure (21). Adverse events of mouthpiece have been described, such as increased salivation, orthodontic problems, gastric distention caused by swallowed air, and nose leaks (19, 20). In case of nose leaks, nasal clips may be used. Mouthpiece ventilation is not possible in case of poor cooperation or in case of severe bulbar dysfunction (19).

Customized masks, available in some specialized centers with the appropriate expertise, may be useful, especially for children under 2 years, and with craniofacial malformations. These interfaces are described as more comfortable, leading to less skin lesions and having the potential to increase ventilation efficacy (22–24). The growing availability of 3D medical printing leads to the development of 3D-printed custom masks for adults and children (25, 26).

Some authors report the use of modified nasal cannula for non-compliant children using CPAP (27).

Finally, headgear should be considered as important as the mask. A well-fitted headgear maintains the mask in place with restraining straps made of soft material that allows sweating (10), and it is usually attached by adhesive strips, hooks, or magnetic pieces, which are easy to manipulate. Straps must be sufficiently tightened to prevent air leaks but with caution, in order to avoid pressure-related skin lesions and disturbed facial growth (23).

Adverse Events

Adverse events related to interfaces are common and may have serious consequences and compromise adherence and ventilation efficacy (5, 23). Changing the interface should be considered if there is any evidence of discomfort, skin lesions, high unintentional leaks, or disturbed facial growth (28). The most frequent adverse events and suggested corrective measures are summarized in **Table 2**.

Nasal, Eye, and Oral Symptoms

Eye symptoms such as discomfort or redness may occur with mask leaks. Mask fitness should be checked and the interface repositioned (5).

Dryness of nose and mouth is a frequent complain during NIV (29), and it is often associated with mouth leaks (30).

TABLE 1 | Advantages and disadvantages of interfaces.

Interface	Characteristics	Advantages	Disadvantages
Nasal mask	Flow through the nose	Allows eating, speaking, secretion management, and using pacifier Several pediatric and infant models and sizes available No risk of aspiration	Risk of: • Nasal dryness and irritation • Mouth leaks • Skin lesion over the nasal bridge and face • Midfacial hypoplasia • Eye irritation in case of leaks
Oronasal mask	Flow through the mouth and nose	No mouth leaks Less risk of midfacial hypoplasia	Limit eating, speaking, secretion management No use of pacifier Risk of: • Aspiration • Suffocation • Skin lesion over the nasal bridge and face • Eye irritation in case of leaks Claustrophobia Few pediatric sizes available
Full facial mask	Flow through the mouth and nose	No mouth leak Less risk of: Facial growth impairment Skin lesion	Limit eating, speaking, secretion management Risk of: • Aspiration • Suffocation • Claustrophobia Few pediatric sizes available Increased dead space Limited domiciliary indications
Nasal pillow	Flow through the nose	Minimal facial contact Allows eating, speaking, and secretion management Less risk of skin lesion No risk of aspiration	Risk of: • Nasal symptoms • Nostrils pain and lesions • Mouth leak No pediatric sizes available
Mouthpiece	Flow through the mouth	Allows eating, speaking, and secretion management Allows air stacking No need of headgear No risk of: • Skin lesion • Aspiration • Nasal symptoms • Claustrophobia Better appearance	Needs a collaborative patient Needs capacity of lips seal Risk of: • Mouth and nose leak • Orthodontic problems • Gastric dilatation • Increased salivation • Vomiting

When mouth leaks occur, nasal function of heating and humidifying the airflow is overcome by the unidirectional flow, resulting in nasal tissue inflammation and increased nasal resistance, leading to patient discomfort (31). Decreasing mouth leaks will alleviate the symptoms. The use of a humidifier reduces nasal discomfort and promotes nasal respiration (32).

Nasal topical treatments such as nasal rinses, topical corticosteroids, or decongestants have been described as being effective in controlling symptoms (5), but there is no clear evidence to support it.

Air Leak

Unintentional leaks, occurring between the face and the mask or through the mouth, may have a deleterious effect on NIV and CPAP treatment (33). They may contribute to patient's ventilator asynchrony, autocycling, and inefficient pressurization and volume delivery, all leading to ventilation and sleep disturbance (34, 35) Domiciliary ventilators are designed to compensate for leaks, but their performance depends on the ventilatory modes and the volume of leaks. Different ventilators have shown considerable variation in their ability to compensate leaks, particularly in pediatric patients (36). Bench studies have

TABLE 2 | Interface-related adverse events and suggested correction measures.

Adverse events	Suggested correction measures
Nasal, eye, and mouth symptoms	Check mask fit
	Consider topical nasal treatment (nasal rinse, corticosteroids, and decongestants)
	Use a humidifier
	Avoid mouth leak: • Change to an oronasal mask (in patients who are able to take the mask off) • Use chin straps • Use a pacifier, in infants
Air leaks	Check mask size, fit, and integrity
	Check headgear fit and integrity (customize it, if necessary)
	If mouth leak: • Change to an oronasal mask (in patients who are able to take the mask off) • Use chin straps • Use a pacifier in infants
	Mouthpiece ventilation: • Use a nasal clip • Use a lip seal
Skin breakdown	Check mask position, size, fit, and integrity
	Alleviate mask pressure
	Hold the tube to diminish movement
	Re-assess the need of humidification or reduce it
	Change interface
	Rotate interfaces
	Apply hydrocolloid wound care dresses
Midfacial hypoplasia	Alleviate mask pressure
	Change interface
	Reduce ventilation hours

also shown that dynamic leaks interfere with tidal volume and leak estimation of the ventilators' monitoring software (37).

Mouth leaks lead to mucosal dryness and increased nasal resistance due to reduced humidification, disturbed ciliary activity, and increased mucus secretion (30). These in turn generate a vicious cycle and further sustain mouth leaks. As a consequence, ventilation performance is compromised, treatment fails to provide relief, and treatment adherence is reduced (30).

A first step in controlling leaks is to assess the mask fitting, looking for mal-positioning or deterioration. It may be useful to ask the patient or the caregiver to put the mask in the presence of one member of the health-care team in order to check the correct fitting. The headgear should also be inspected for integrity or strap laxity and be substituted if necessary. In case of mouth leaks, using a pacifier in infants and a chin strap in older children or switching to an oronasal mask may resolve the problem (38). The inclusion of a humidifier in the circuit may help in decreasing nasal resistance and mouth breathing, thus attaining more comfort (39).

Skin Breakdown

Skin lesions are frequent adverse events associated with NIV masks (9). Since impermeable silicone polymers are the most frequently used contact materials, increased humidity can provoke skin maceration and, consequently, increased risk of cutaneous lesions (8).

A pressure ulcer (PU) is defined as a local of skin lesion due to pressure, shear, or friction (40). Medical device- related PU results from the use of devices designed and applied for diagnostic or therapeutic purposes (41). PU is more frequent in locations with less subcutaneous tissue like the cheeks, chin, forehead, and nasal bridge (42).

Excessive pressure exerted by the mask, causing tissue ischemia, is the most important risk factor for skin and facial side effects (43). Besides the mechanical effect of pressure associated with straps tension, an increase in inflammatory cytokines in affected skin has been shown (43). An increase in temperature and humidity detected below the mask eases skin maceration and potentiates mechanical effect of friction, contributing to the development of PUs (43, 44). Skin lesions may be further aggravated by poor nutrition and the loss of muscular mass, making neuromuscular patients more susceptible to this kind of complications (34). The humidification of NIV circuits may also contribute to skin lesions by increasing skin moisture (9).

In pediatric patients, the risk factors for PUs are skin immaturity, decreased/reduced mobility, altered neurological status, and the use of masks that are too small or do not fit to the facial anatomy of the child, as what happens in children with craniofacial anomalies (44, 45).

Use of protective dressings between the skin and the mask is common but controversial in literature. In adult patients, it was shown that hydrocolloid materials, which adhere to the skin, increase mask adherence and reduce friction, have a protective effect on mask skin lesions, and contribute to improvements in temperature control and skin barrier function (40). A meta-analysis of 22 studies, three of them included pediatric patients, has shown that hydrocolloid dresses were significantly more effective in preventing PU than gauze or standard skin care (46). The use of these materials as soon as skin redness appears is advised (9). However, not all types of protective patches were shown to prevent skin injury. Therefore, selection of the most suitable mask and headgear, fixation with an optimal tension, and frequent inspection for skin alterations represent key elements for effective PU prevention (45).

The risk of PU may be reduced by appropriate mask type and size selection and by changing or alternating interfaces with different pressure points. Adequate tightness of headgear strains may be checked by passing one finger

between the face and the headgear straps in each side of the face (34).

LTNIV health-care team should educate patients and caregivers to pay careful attention to skin integrity in order for early identification of any skin breakdown and take immediate actions to prevent severe lesions.

Midface Hypoplasia

Midface hypoplasia is a motive of concern in pediatric LTNIV because continuous pressure over the face in a growing child leads to the molding of the underlying structures and alterations in face development, which may cause airway narrowing and thus aggravate obstructive sleep apnea (23, 47).

In a series of 40 children, facial flattening was identified in 68% patients (23). No correlation was found between facial flattening and age, type of mask, or daily ventilation, but it was more frequent in obstructive sleep apnea and neuromuscular patients who were younger and whose daily ventilator support requirements were longer. A retrospective study in children with craniofacial malformations requiring LTNIV for obstructive sleep apnea, comparing characteristics of compliant and non-compliant patients, found that compliant children showed more facial growth restriction (47).

Changing the interface periodically, alternating pressure points, alleviating the pressure of the headgear (without compromising mask-face seal), and reducing the number of ventilation hours may help to reduce facial growth restriction (23, 38).

Select an Interface

Interface choice depends on several factors, including age and neurocognitive development, craniofacial anatomy, specific disease's characteristics, severity of respiratory disturbance, selected ventilator, health team experience, and child's and caregiver's preference (5, 11). When choosing and fitting an interface, ample care should be taken to ensure patient's familiarity with the equipment and comfort, since prompt symptom relief and comfort increase adherence to treatment (48).

What are the steps to select a mask?

- Take some time with the child and caregivers to explain the ventilation therapy, objectives, indications, and contraindications.
- Consider the age, disease, type of ventilation, ventilator, and circuit to select ventilated or non-ventilated masks. Nasal masks are the most used interface in pediatric patients. Infants and younger children are essentially nasal breathers, and most of commercially available pediatric masks are actually nasal interfaces (49). The use of oronasal masks and nasal pillows is limited by the limited availability of pediatric sizes. Mouthpiece ventilation may be prescribed to older and cooperative children who need daytime ventilation.
- Have several masks available to test the most adequate one. Consider the child's and caregivers' preferences in the decision process.
- Evaluate the headgear: in small children or children with craniofacial anomalies, some adjustments may be necessary.
- Initiate ventilation to evaluate leaks and mask fitness. Identify pressure points and anticipate measures in order to prevent skin lesions.
- In anxious or young children, as well as in those with neurocognitive disability, it may be important to let the child take the mask home some days before initiating ventilation, for familiarization with the equipment.
- Be prepared to change the interface if needed, especially in the first days of treatment.

Behavioral therapy has been shown to be effective in increasing interface tolerance in children not compliant (50), especially in younger and neurocognitive-compromised patients (51). Some anecdotal reports describe the use of medical hypnosis as a valuable tool to reduce anxiety in children and parents (52).

CIRCUITS

Circuits are tubing systems that connect the ventilator to the interface and have the role to deliver positive air pressure to the patient's airways, allowing clearance of exhaled air. There are three types of circuits. The double-limb circuit consists of an inspiratory tube and an expiratory tube with inspiratory and expiratory valves at the proximal end and a Y-shaped ending at the distal end just proximal to the interface. The single-limb circuit consists of a single tube. Since such an assembly could cause mixing of the inspiratory and expiratory air and consequently leading to CO_2 rebreathing, an expiratory valve or an intentional leakage system is incorporated into the circuit. The former is termed "non-vented" and the latter "vented" circuit. In the first case, the expired air leaves the tube through an expiratory valve positioned at the circuit's distal end. In the second assembly, an intentional leak at the distal end of the tube or in the interface itself allows for adequate exhaled air washout (11, 53).

A double-limb circuit, a non-vented single-limb circuit with a distal expiratory valve, or a vented single-limb circuit can be used in combination with non-vented masks. Currently, the large majority of masks and prongs are of the vented type. Holes in masks are more effective than exhalation valves to prevent CO_2 rebreathing (54). If zero positive end-expiratory pressure (PEEP) condition is required, only a double-limb circuit or a single-limb circuit with an actively driven exhalation valve can be used.

HUMIDIFIERS

NIV provides unidirectional airflow, often at high flow rates. Even though nasal interfaces are predominantly used and consequently the air tempering actions of the nasal airway is preserved, such artificial conditions often cause nasal irritation, increase nasal resistance, compromise mucociliary clearance, reduce tidal volume, and finally, compromise NIV compliance (55, 56).

Heated humidification decreases nasal resistance and its deleterious effect on tidal volume, it increases patient comfort

and adhesion to NIV (56), and it has been advised for improvement in compliance to CPAP in adult patients (57).

Humidifiers may be interposed in the ventilatory circuit, when indicated. Mechanical ventilation utilizes two types of humidification. Active humidification consists of a heated humidifier, which requires an external source of heat and water. Alternatively, passive humidification is attained by a heat and moisture exchanger (HME), interpositioned into the respiratory circuit at the location where heat and humidity of the air exhaled can be caught and subsequently passed to the next inhalation (32). The first heating modality is often preferred in LTNIV, as it can provide smaller dead space, reduce the work of breathing, and also be effective in air conditioning (55). Heated humidifiers may be internal (built into the ventilator) or external (connected to the ventilator by tubing) (58). Internal humidifiers have less impact on ventilator performance (58).

Inhaled air temperature and humidity should be set to the level most comfortable to the patient (39). Since ambient conditions vary, modifications of the humidification settings need to be foreseen. In a cold environment, relatively overheated air may precipitate vapor condensation in the tubing, thus leading to suboptimal NIV performance. Some ventilators integrate humidifiers combined with heated tubes, which allow automatic control of humidity and air temperature according to ambient variations (59).

Addition of a humidifier may increase NIV comfort and compliance, when patients complain about nose and mouth dryness or irritation. Special care needs to be taken in small children, since additional humidity may increase secretions and thus compromise their airway patency (60).

Water vapor condensation in the tube may be reduced by covering the tubes with a cloth, placing them under the bedding, or using heated circuits with integrated heated wires that have been recently described to contribute to a better sleep quality and adherence to NIV therapy (61).

It needs to be considered that humidifiers may increase the respiratory circuit's resistance and dead space, interfering with ventilator's triggering and pressurization. Therefore, efficacy of provided ventilatory support should be reevaluated in case a humidifying system is installed (56).

CLEANING AND DISINFECTION

There is a lack of clear guidance on home ventilation equipment cleaning. Dirty circuits and masks are more prone to be contaminated with bacteria, leading to a higher risk of patient's bacterial colonization (62). Nevertheless, a study found that the type of ventilator, total daily time of ventilation, and the presence of humidifier did not seem to be associated with equipment's bacterial contamination (63).

In a pilot study of 52 ventilated patients, which included 12 children, the authors found the cleaning of the masks to be highly variable, reaching an average 2.9 (0–7) times per week, and only rarely to be disinfected. Bacterial contamination was identified in only 16% of participants. The same bacteria were isolated from the mask and sputum in a cystic fibrosis patient (64).

Washing all components twice monthly in the dishwasher has been shown to be effective in cleaning masks and circuits. When not available, hot water and detergent will be sufficient. After washing, every component must be dried in room air (65).

If a patient is particularly susceptible to respiratory infections, disinfection with 0.5% hypochlorite solution may be indicated (65).

FOLLOW-UP

At every follow-up visit, mask fitting, adverse events, and equipment hygiene should be checked and reviewed. Careful attention to the patient and/or the caregiver complaints is crucial in order to increase patient satisfaction and comfort and ultimately the adherence to treatment. The ventilation team should be vigilant and proficient in delivering solutions for inadequate ventilation or patient's discomfort.

FUTURE RESEARCH

In the last few years, research on LTNIV in children has increased, but there are still significant gaps in our knowledge and equipment availability. Although the availability of nasal masks has increased for infants and small children, oronasal masks and nose pillows do not exist for these age groups. Further investigation on mask exerted facial pressure points and newer materials is needed. Advancements in 3D printing of affordable individually customized masks could have an important role in reducing severe adverse events in patients with craniofacial abnormalities. The role of humidification in pediatric LTNIV needs further validation. The impact of different interfaces, circuits, and humidifiers in ventilators' performance in pediatric age also needs to be addressed in future research.

CONCLUSION

Correct choice of the interface is essential for ventilatory support efficacy and compliance. Although nasal masks are the most frequently used in pediatric age, there are no guidelines on the choice of an optimal interface. Similarly, the guidance on humidification use in children on LTNIV is scarce. Early and careful attention must be paid to any sign of adverse events, patient's discomfort, or suboptimal ventilation in order to attain the best therapy results.

AUTHOR CONTRIBUTIONS

RF has made the literature search and elaborated the manuscript.

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MINI REVIEW
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Long Term Continuous Positive Airway Pressure and Non-invasive Ventilation in Obstructive Sleep Apnea in Children With Obesity and Down Syndrome

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This review will focus on non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) therapy in children with obstructive sleep apnea (OSA) due to obesity and underlying syndromes. These children have a high prevalence of OSA and residual OSA after adenotonsillectomy. Therefore, a high proportion of these children are treated with CPAP or NIV. This review will focus on treatment selection tools and will subsequently cover specific issues on CPAP treatment in obese and syndromic children with a major focus on Down syndrome.

Keywords: obstructive sleep apnea, obesity, down syndrome, continuous positive airway pressure, non-invasive ventilation

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a manifestation of sleep-disordered breathing (SDB) in children. OSAS is characterized by prolonged episodes of increased upper airway (UA) resistance and respiratory effort with partial (obstructive hypopnea) or complete (obstructive apnea) UA obstruction during sleep. The syndrome is often associated with snoring, intermittent hypoxia, hypercarbia, and/or sleep disruption. Additionally, OSAS is associated with a number of significant complications such as daytime neurobehavioral problems, learning deficits, growth retardation, and cardiovascular complications and it should therefore be correctly treated (1, 2).

Structural narrowing of the UA in combination with inadequate compensation for a decrease in UA neuromuscular tone is an important factor in the pathogenesis of OSAS (3, 4). Adenotonsillar hypertrophy is the most important predisposing factor for UA narrowing in otherwise healthy children. However, many other causes of craniofacial defects may coexist such as maxillary and mandibular deficiency, tongue, and soft palate enlargement, and inferior displacement of the hyoid bone (3). Additionally, the pathogenesis of UA narrowing is more complex in certain subgroups such as children with obesity, craniofacial malformation, Down syndrome or neuromuscular disorders. The complexity of the pathogenesis of OSAS in these children is illustrated by a high incidence of residual OSAS after adenotonsillectomy (AT) and by a frequent need for additional treatment. For instance, residual OSAS after AT is reported in 54–88% of obese children compared to 15–26% in non-obese children (5–7). Lumeng et al. (8) also demonstrated that the prevalence of OSAS in these subgroups is markedly increased compared to the prevalence of 1–4% in the general population (8). Obese children have a prevalence ranging from 13 to 59% (9), children suffering

from Down syndrome 30–100% (10–14), achondroplasia 54% (15, 16), craniofacial syndromes such as Pierre-Robin sequence 85% (17) and non-syndromic cleft palate 8, 5% (18).

In view of the high prevalence of OSAS and residual OSAS after adenotonsillectomy, a high proportion of these children are treated with continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV). CPAP or NIV is not a first line treatment in these children. In general, it is reserved for children with residual OSA after adenotonsillectomy or other upper airway surgery or in those children who are not surgical candidates. In our opinion, the setting for upper airway surgery should also be set correctly as obesity or Down syndrome are also associated with post-operative complications (1). Therefore, it is critical to identify the anatomical site(s) responsible for obstruction in the upper airway and to couple these findings with the most appropriate treatment. Treatment can consist of (a combination of) weight loss, anti-inflammatory medication, orthodontics, (adeno) tonsillectomy, supraglottoplasty, lingual tonsillectomy, other upper airway surgery or CPAP/NIV most often in the context of multilevel obstruction. This review will briefly focus on these treatment selection tools and will subsequently cover specific issues on positive airway pressure (PAP) treatment in obese and syndromic children with a major focus on Down syndrome.

TREATMENT SELECTION: HOW TO SELECT BETWEEN SURGERY VS. NIV?

The European Respiratory Society published two consensus statements from a multidisciplinary expert group describing a diagnostic and treatment algorithm for OSAS in infants and children (1, 2). Especially in infants where adenotonsillar hypertrophy is not yet the predominant cause of UA obstruction, UA endoscopy and imaging are routinely used to identify the anatomical site(s) of UA obstruction. However, it has to be noted that only a limited number of studies with a small sample size evaluated the diagnostic value of endoscopy in infants. Laryngomalacia is a frequent abnormality detected by endoscopy in children with Down syndrome and upper airway obstruction (19). Bravo et al. (20) and Cheng et al. (21) performed endoscopic evaluation in a total of 58 young children (1 month-4 years old) with Pierre Robin sequence. The degree of upper airway obstruction was assessed at the velopharyngeal, oropharyngeal, and tongue base level. Presence of moderate or severe obstruction was 87% sensitive and 100% specific in predicting an obstructive respiratory disturbance index >5 episodes/h (20). Sher et al. (22, 23) described 4 types of pharyngeal airway obstruction in infants and children with various craniofacial abnormalities including craniosynostosis and Pierre Robin sequence: posterior movement of the tongue toward the posterior pharyngeal wall (type I); compression of the soft palate on the posterior pharyngeal wall by the tongue (type II); collapse of the lateral pharyngeal walls (type III); circular constriction of the pharynx (type IV).

In older children, drug induced sleep endoscopy (DISE) and/or imaging are mainly used in the setting of residual OSAS post-adenotonsillectomy. DISE in children with persistent SDB may demonstrate laryngomalacia, adenoidal tissue regrowth, tongue base obstruction, and pharyngeal collapse (16, 24–26). MRI of the upper airway may reveal residual adenoid tissue in obese children with persistent OSAS following adenotonsillectomy (27). Regrown adenoidal tissue, glossoptosis, hypopharyngeal collapse, soft palate collapse, and hypertrophic lingual tonsil are abnormalities that may be identified by cine MRI in children with Down syndrome and persistent SDB after adenotonsillectomy (28, 29).

Although there is a lack of clinical trials concerning this topic, all children with moderate-to-severe OSAS undergo DISE in our center to guide further treatment. This certainly provides more insight into the pattern of UA obstruction in the individual patient. For instance, a study from our group in surgically naïve children with Down syndrome found that the majority of these subjects presented with obstruction at the levels of the adenoids and tonsils. However, 85% of subjects also presented with multilevel collapse which most likely explains the high percentage of residual OSAS after adenotonsillectomy in this cohort (52%) (30).

In summary, obesity and the presence of craniofacial malformations or syndromic conditions are major risk factors for residual OSAS. Upper airway evaluation by means of DISE and cine MRI may identify lingual tonsillar hypertrophy and laryngomalacia as the most common anatomical correlates for residual disease. These methods may guide the clinicians to specific surgical interventions or non-surgical treatment modalities such as weight loss, orthodontic treatment, medical treatment and myofunctional therapy and toward CPAP or NIV treatment. An overview of this approach is presented in **Figure 1** (31).

CPAP IN OBESE CHILDREN

Concerning sleep apnea in the context of pediatric obesity, it remains crucial that the child is followed up in a multidisciplinary obesity treatment program. It is important to note that limited data from cohort studies generated from residential treatment centers or reports on bariatric surgery have shown that weight loss is beneficial for OSA (32–34). However, the effects of weight loss on an outpatient basis (35) and in young obese children remain little studied. Furthermore, adenotonsillectomy as a treatment for OSA in obese children is frequently associated with weight gain and treatment failure (36). In summary, it is crucial to emphasize the importance of weight management in the context of the obese child with OSA. However, weight loss takes time and compliance can be challenging and therefore these children are often referred for CPAP therapy in the context of moderate-to-severe OSA. There is limited data on the prevalence obese subjects entering an obesity clinic and needing CPAP therapy. A recent study from Spain in 113 obese children found an OSA prevalence of 55%. Out of the 62 subjects with OSA, 10 were started on CPAP corresponding to an incidence of 16%. Indication for CPAP was defined as moderate-to-severe

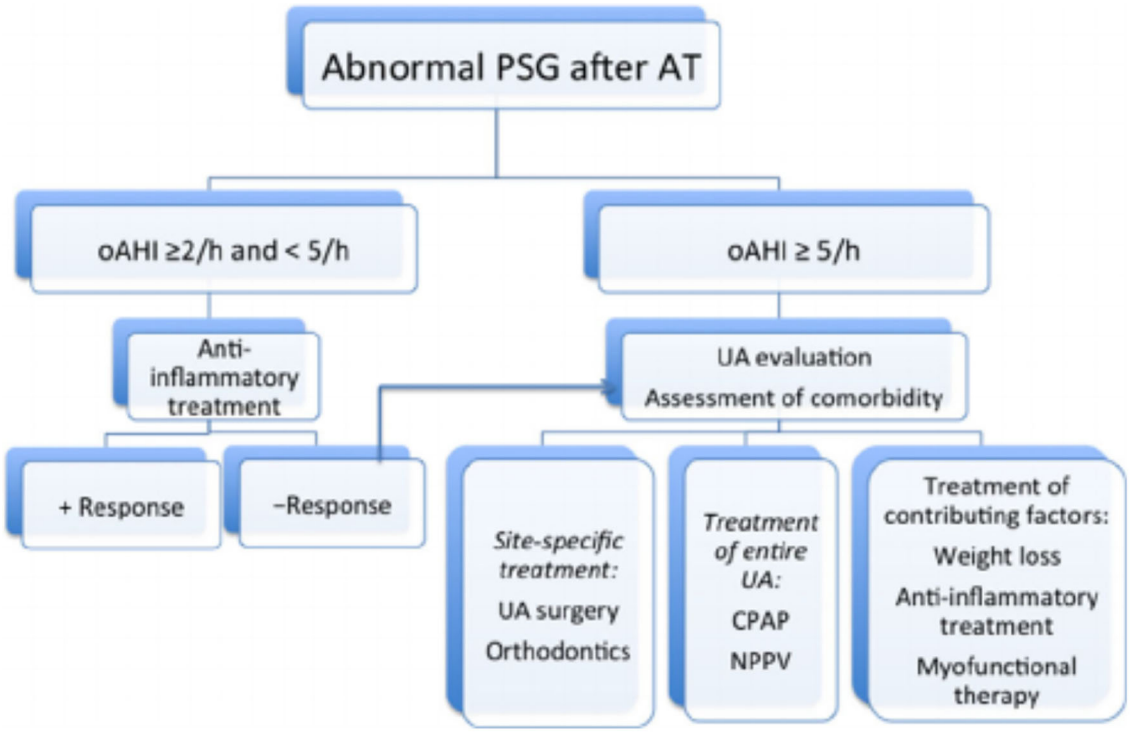

FIGURE 1 | Proposed algorithm for the management of persistent OSA post-adenotonsillectomy (31).

OSA defined as ASI > 10 without endoscopic evidence of adenotonsillar hypertrophy (37).

Adherence to treatment is a general issue in obese patients and this seems also true for obese children and adolescents requiring CPAP therapy. Marcus et al. (38) compared CPAP adherence between children on bilevel positive airway pressure with pressure release technology (Bi-Flex) and a group on standard CPAP therapy. Fifty six children were included, and the vast majority of these patients were obese. Most subjects attempted to use their ventilation on most nights, with the devices being turned on more than two-thirds of the nights during the first month of therapy. However, the average nightly use varied widely between subjects, ranging from 1 to 536 min/night for the first month and decreased during the following months (38). Another study on adherence by the same group investigated predictors of adherence in a similar cohort. Obesity was not an independent predictor of adherence. Lower maternal education was the strongest predictor of poor adherence, with older, typically developing youth, and African American youth less adherent to CPAP therapy as well. Lower levels of social support were also associated with poor adherence (39). An Australian cohort showed better adherence rates. However, this study noted that 50% of the 35 cases who did not continue in the current study for CPAP were overweight or obese and their failure to comply with therapy commenced very early in the process (i.e., before therapy initiation) (40). Pury et al. (41) studied a cohort of 56 children with a mean age of 13 years and 65% of the studied subjects were obese. CPAP use was the highest at week 1 (used 79% percent of nights), then declined over time: 65% of nights at month 1 and 57% of nights at 3 months, with wide individual variation. Average nightly PAP use also declined over time: from 3.5 ± 2.7 h at week 1 to 2.8 ± 2.4 h at month 3. CPAP was use was better if another family member was also on CPAP, obesity did not affect CPAP adherence (41). Amaddeo et al. (42) studied out-patient initiation of CPAP therapy in children and showed a general high level of adherence in their cohort of 31 children (3 were obese).

Limited research has been published on the effects of CPAP therapy on metabolic and cardiovascular comorbidities of pediatric obesity. Sundaram et al. (43) studied the effects of CPAP therapy in subjects with non-alcoholic fatty liver disease. Nine patients were treated with CPAP for ∼3 months with relatively good adherence (73% adherence of total days prescribed and a mean usage per day of 296 ± 126 min). With CPAP treatment, participants had an increased duration of sleep (total sleep time), and repeat polysomnography demonstrated improvement in OSA severity. Their results showed that CPAP improved the severity of liver injury and also selected markers of the metabolic syndrome and reduced oxidative stress. This effect was independent from BMI which even increased during the course of the study (43). This last finding is intriguing and clinically relevant suggesting increased energy expenditure during sleep (32). Alonso-Alvarez et al. (37) studied the effects of different OSA treatments on several markers of the metabolic syndrome. Only a limited number of patients on CPAP were included. This might explain why no significant effects of CPAP directly on

metabolic markers were observed (37). Another small-scale study in 11 obese children on CPAP therapy only found a change in leptin levels on CPAP treatment (44).

In summary, we can conclude that OSAS in pediatric obesity is highly prevalent. The pathophysiology is multifactorial, but these children need to be included in a multidisciplinary weight management program in context of the several other obesity-related complications. Weight loss can improve OSAS, but CPAP is indicated in children with moderate-to-severe OSAS in whom surgery is not indicated. Adherence can be an issue in these subjects and these subjects need to be followed closely. The effects of CPAP on cardiovascular and metabolic complications in obese children and adolescents require more study.

CPAP IN CHILDREN WITH DOWN SYNDROME

Our group has published on the incidence of CPAP therapy in children with Doqn syndrome. Maris et al. (30) studied DISE-directed therapy in 41 surgically naïve children with Down syndrome and OSA. Seven percentage of of patients were directly referred to CPAP therapy. Twenty five children underwent (adeno) tonsillectomy but with a high percentage (∼50%) of persistent OSA. The majority of these patients had multilevel collapse on DISE. One of these patients was also referred for CPAP therapy (30).

Published research regarding CPAP in Down syndrome is somewhat limited. Trucco et al. (45) described 39 patients (out of a total group of 60) with different kinds of respiratory support: 14 patients on supplemental oxygen, 18 on CPAP, and 7 on bilevel NIV. Median age at initiation of respiratory support was 2.4 years old (interquartile range 0.7–6). Twelve children out of 60 were referred for a sleep study because of OSAS symptoms persisting after adeno-tonsillectomy, while 48 did not receive any surgery at the time of the sleep study. All of the 12 referred post-adenotonsillectomy patients had evidence of significant OSAS requiring ventilatory support. Six started CPAP and three bilevel NIV while two were started on oxygen for lack of tolerance to positive pressure support and one child could not tolerate even nasal cannula with additional oxygen. Out of the 48 surgical naïve patients, 22 out of the 23 children diagnosed with sleep-disordered breathing were started on respiratory support first-line: 10 commenced CPAP, 2 bilevel NIV, 10 required overnight O2 for low overnight saturations or central apneas, whereas 11 patients were referred for adenotonsillectomy after which 6 went on to require initiation of positive pressure therapy for evidence of residual OSAS. After a median of 4 months after initiation of respiratory support, 22 out of 39 (56%) were considered as regular users. Oxygen was reported to be tolerated by 9 out of 14 subjects (64%), 9 out of 18 patients (50%), and 4 out of 7 (57%) had satisfactory adherence to CPAP and bilevel NIV, respectively. The mean CPAP use was 5 h, and median bilevel NIV use was 8 h. Adherence at the latest evaluation, after ∼2 years, was reported as good in 6 out of 9 (67%) patients on O2, in 7 out of 18 (39%) patients on CPAP, and in 4 out of 6 (67%) on bilevel NIV (45). Dudoignon et al. (46) described 19 patients on CPAP or NIV therapy. Patients on CPAP or NIV therapy had more severe sleep apnea compared to patients who did not need respiratory support. The mean age at CPAP/NIV initiation was 7 ± 7 years with a wide range (0.4–23 years). Mean duration of treatment at the time of the study was ∼2 years. CPAP/NIV adherence was available only in 11 patients, mainly because of a too young age in 4 patients which did not allow an accurate interpretation of actual ventilator use. Adherence was good with an average use per night of almost 9 h and 9/11 patients using CPAP/NIV $>$ 4 h/night. Three patients could be successfully weaned from CPAP/NIV. Finally, no complications were observed with CPAP/NIV (46). Sudarsan et al. (47) compared adenotonsillectomy vs. CPAP in Down syndrome patients with OSA. In the CPAP group, 36 subjects completed the study. Five subjects had persistent OSA (defined as AHI $>$ 1 corresponding to a failure rate of 14%). Children receiving CPAP or adenotonsillectomy had similar improvements in symptoms, quality of life and AHI (47).

Along these lines, adherence issues are frequently encountered. Fortunately, adherence tends to be a greater issue when beginning therapy, and consistent usage can often be achieved with time. For instance, the study by Dudoignon et al. (46) showed that 81% of patients had CPAP usage $>$ 4 h per night 1–3 years after starting therapy. An alternative in patients with CPAP intolerance could be switching to high flow nasal cannula therapy (48) or switching to this interface coupled to a regular ventilator (49). Amaddeo et al. (48) studied HFNC in 8 patients who were intolerant to CPAP (6 patients had Down syndrome). Three out of the 6 patients with Down syndrome were successfully managed with HFNC, the other patients did not tolerate HFNC as well. These three patients all had severe neurocognitive and behavioral impairment (48).

CONCLUSION

OSAS in children with obesity and underlying syndromes is highly prevalent. Treatment selection is critical, to limit unsuccessful surgery and in view of the high prevalence of residual OSAS after adenotonsillectomy. Therefore, a high proportion of these children are treated with CPAP or NIV. Overall, PAP therapy has beneficial effects on sleep parameters, daytime symptoms, quality of life, and metabolic parameters. However, these data are generated from a limited number of studies and more studies on the effects of CPAP are certainly warranted. Compliance can be an issue in obese children and patients with Down syndrome for instance, however an intensive initial follow-up can certainly be helpful in these cases. The use of HFNC certainly deserves more study in CPAP intolerant patients.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Non-invasive Ventilation in Children With Neuromuscular Disease

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The respiratory muscles are rarely spared in children with neuromuscular diseases (NMD) which puts them at risk of alveolar hypoventilation. The role of non-invasive ventilation (NIV) is then to assist or "replace" the weakened respiratory muscles in order to correct alveolar hypoventilation by maintaining a sufficient tidal volume and minute ventilation. As breathing is physiologically less efficient during sleep, NIV will be initially used at night but, with the progression of respiratory muscle weakness, NIV can be extended during daytime, preferentially by means of a mouthpiece in order to allow speech and eating. Although children with NMD represent the largest group of children requiring long term NIV, there is a lack of validated criteria to start NIV. There is an agreement to start long term NIV in case of isolated nocturnal hypoventilation, before the appearance of daytime hypercapnia, and/or in case of acute respiratory failure requiring any type of ventilatory support. NIV is associated with a correction in night- and daytime gas exchange, an increase in sleep efficiency and an increase in survival. NIV and/or intermittent positive pressure breathing (IPPB) have been shown to prevent thoracic deformities and consequent thoracic and lung hypoplasia in young children with NMD. NIV should be performed with a life support ventilator appropriate for the child's weight, with adequate alarms, and an integrated (±additional) battery. Humidification is recommended to improve respiratory comfort and prevent drying of bronchial secretions. A nasal interface (or nasal canula) is the preferred interface, a nasobuccal interface can be used with caution in case of mouth breathing. The efficacy of NIV should be assessed on the correction of alveolar ventilation. Patient ventilator synchrony and the absence of leaks can be assessed on a sleep study with NIV or on the analysis of the ventilator's in-built software. The ventilator settings and the interface should be adapted to the child's growth and progression of respiratory muscle weakness. NIV should be associated with an efficient clearance of bronchial secretions by a specific program on the ventilator, IPPB, or mechanical insufflation-exsufflation. Finally, these children should be managed by an expert pediatric multi-disciplinary team.

Keywords: non-invasive ventilation, child, neuromuscular disease, nocturnal hypoventilation, sleep, sleep-disordered breathing, home treatment

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INTRODUCTION

Long term non-invasive ventilation (NIV) involves the delivery of ventilatory assistance through a non-invasive interface, as opposed to invasive ventilation via a tracheostomy. Children with neuromuscular disease (NMD) represent the largest group of children requiring long term NIV (1). Indeed, the respiratory muscles are rarely spared in children with NMD which puts them at risk of alveolar hypoventilation, especially during sleep. The role of NIV is then to assist or "replace" the weakened respiratory muscles in order to correct alveolar hypoventilation by maintaining a sufficient tidal volume and minute ventilation (2). Despite the large use of NIV in children with NMD, there is a lack of validated criteria to start NIV and follow up relies mainly on experience and practice (1, 2). NIV is associated with a correction in night- and daytime gas exchange, an increase in sleep efficiency and an increase in survival but data on quality of life are scarce (1, 3–6). In children, the technological aspects of NIV are crucial with the need of regular adaptations according to the patient's age and disease progression. This review aims at giving an update on the different aspects on NIV in these severely disabled children and underlines the importance of a management and follow up by an expert pediatric multidisciplinary team.

WHY MAY SOME CHILDREN WITH NEUROMUSCULAR DISEASE NEED NIV?

In healthy subjects, the respiratory load, i.e., the effort the subject has to perform to generate a breath, is low, the capacity of the respiratory muscles is normal, and the central drive appropriately commands the respiratory muscles (**Figure 1**). In disorders characterized by a weakness of the respiratory muscles as observed in NMD, the central drive increases its demands of the respiratory muscles. However, when the respiratory muscles are not able to cope with the respiratory load, hypoventilation, defined by hypercapnia and hypoxemia, occurs. NMD that involve the motor neuron, the peripheral nerve, the neuromuscular junction, or the muscle may cause excessive respiratory muscle weakness. Kyphoscoliosis, which is common in children with NMD, may increase the respiratory load and cause a mechanical disadvantage of the respiratory muscles, precipitating alveolar hypoventilation.

The most common NMD requiring NIV during childhood are Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA). DMD is a progressive disorder, and ventilatory failure is inevitable in the course of the disease, although the time course of progression to it varies between individuals. Alveolar hypoventilation is also common in children with SMA type I or II. Alveolar hypoventilation is less frequent in other muscular dystrophies, such as Becker, limb-girdle, and facioscapulohumeral dystrophies. Congenital myopathies are often less progressive (7). However, some congenital myopathies such as collagen 6 (COL6) myopathies or selenopathies are characterized by a predominant weakness of the diaphragm, exposing these children to sleep-disordered breathing, although their peripheral muscle strength remains relatively preserved (8, 9). The importance of respiratory failure associated with spinal cord injury depends on the level of the injury. High spinal cord injury, above C3, causes diaphragm paralysis. In patients with lower cervical cord injury, expiratory muscle function is compromised, impairing cough and the clearance of bronchial secretions. As a result, the retention of secretions leading to atelectasis and bronchopneumonia frequently occurs. It has to be noted that the respiratory status of children with NMD may deteriorate with growth because the weakened muscles may be unable to cope with an increasing body mass and metabolic demand.

NIV is a non-invasive ventilator assistance that assists the breathing of the patient by delivering a positive pressure during each inspiration in order to maintain a sufficient tidal volume and minute ventilation. In NMD, the role of NIV is to assist or "replace" the weakened respiratory muscles in order to restore a normal breathing and correct alveolar hypoventilation. In progressive NMD, NIV is initiated and preferentially used during sleep. Indeed, sleep is associated with changes in respiratory mechanics with an increase in ventilation–perfusion mismatch and in airflow resistance and a fall in functional residual capacity (**Figure 2**). Although the activity of the diaphragm is preserved, that of the intercostal and the upper airway muscles significantly decreases. Finally, central drive and chemoreceptor sensitivity are less efficient during sleep than during wakefulness. All these physiological changes explain why the arterial pressure in carbon dioxide ($PaCO_2$) may rise of up to 3 mmHg (0.4 kPa) in healthy subjects. This decrease in alveolar ventilation predominates during rapid eye movement sleep and explains the greater vulnerability of patients with NMD during this sleep stage. The majority of children with NMD need NIV only during sleep (10, 11) but some children with progressive NIV may develop daytime respiratory failure, requiring additional ventilator support during daytime (**Figure 3**) (12).

WHEN SHOULD NIV BE STARTED?

There are no validated criteria to start long term NIV in children (**Figure 3**). In clinical practice, NIV may be initiated in an acute setting, after invasive or NIV weaning failure in the pediatric intensive care unit, in a subacute or chronic setting, on abnormal nocturnal gas exchange alone or on the association of abnormal gas exchange and respiratory events on a polysomnography (1, 13, 14).

In clinical practice, consensus conferences agree on the value of daytime hypercapnia and recurrent acute respiratory exacerbations to initiate NIV because these criteria are the signature of established ventilatory failure (15). But these classical criteria are preceded by a variable period of nocturnal hypoventilation during which treatable symptoms, such as frequent arousals, poor sleep quality, severe orthopnoea, daytime fatigue and alterations in cognitive function, may deteriorate the daily life of the patient (6, 16, 17).

The main challenges or difficulties for NIV initiation in children are thus to define (1) the timing and type of

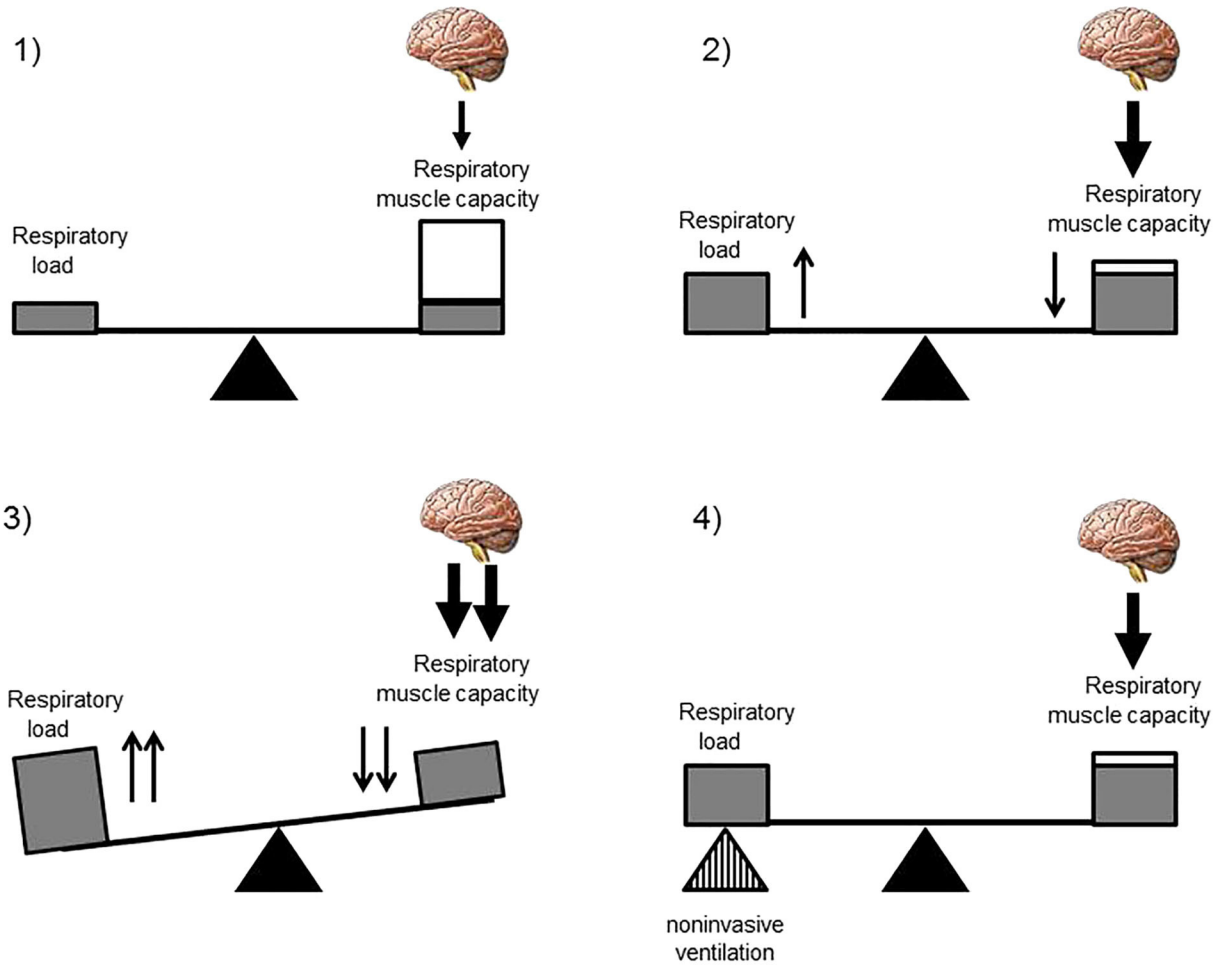

FIGURE 1 | Disequilibrium of the respiratory balance in children with neuromuscular disease. (1) The normal respiratory balance comprises the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive. In a healthy subject, the respiratory load is low, the capacity of the respiratory muscles is normal, and the brain appropriately commands the respiratory muscles. Only a small proportion of the total respiratory muscle capacity is necessary for the breathing process. (2) In children with neuromuscular diseases, the respiratory load is increased and the capacity of the respiratory muscles is decreased. The brain drives the weakened respiratory muscles which need to use a large proportion of their total capacity for the breathing process. (3) Excessive weakness of the respiratory muscles and/or an increase in the respiratory load causes disequilibrium in the respiratory balance which translates into alveolar hypoventilation if the imbalance exceeds a certain threshold. (4) Non-invasive ventilation may correct this disequilibrium by assisting or "replacing" the weakened respiratory muscles.

investigation, such as a polysomnography, a polygraphy, or an overnight gas exchange recording, that should be performed for NIV initiation, and (2) the values or thresholds of the parameters that should be retained for NIV initiation, such as the oxygen (O_2) and/or CO_2 level, and/or apnea-hypopnea index (AHI), with the assumption that their correction will be associated with a benefit of NIV (14). These difficulties are due to the lack of markers of end-organ morbidity associated with sleep-disordered breathing and chronic respiratory failure in children with NMD.

NIV may be justified without a sleep study when the child presents episodes of acute respiratory failure triggered by a respiratory infection or an anesthetic procedure, as these events are markers of an insufficient respiratory reserve (14, 15). Concerning the timing of a sleep study, there is a lack of validated recommendations. This may be in part explained by the heterogeneity of pediatric NMD and the variability of respiratory involvement within a specific disease such as SMA or COL6 myopathies (18, 19). Symptoms of sleep-disordered breathing may be silent or difficult to establish in children because of reliance on parents and second-hand caregivers, who may have difficulties assessing the child's disease and sleep. Children with a progressive NMD tend to underestimate symptoms such as fatigue before using NIV because onset is generally insidious. Most importantly, symptoms suggestive of sleep-disordered breathing did not differ between children with a NMD with or without documented nocturnal hypoventilation (17). Symptoms cannot thus be used as predictors or markers of nocturnal hypoventilation. Lung function parameters are also poor indicators of nocturnal hypoventilation. In patients with NMD, vital capacity (VC) and inspiratory VC have been shown to have some correlation with daytime and nocturnal gas exchange (20, 21). Daytime predictors of nocturnal hypoventilation have

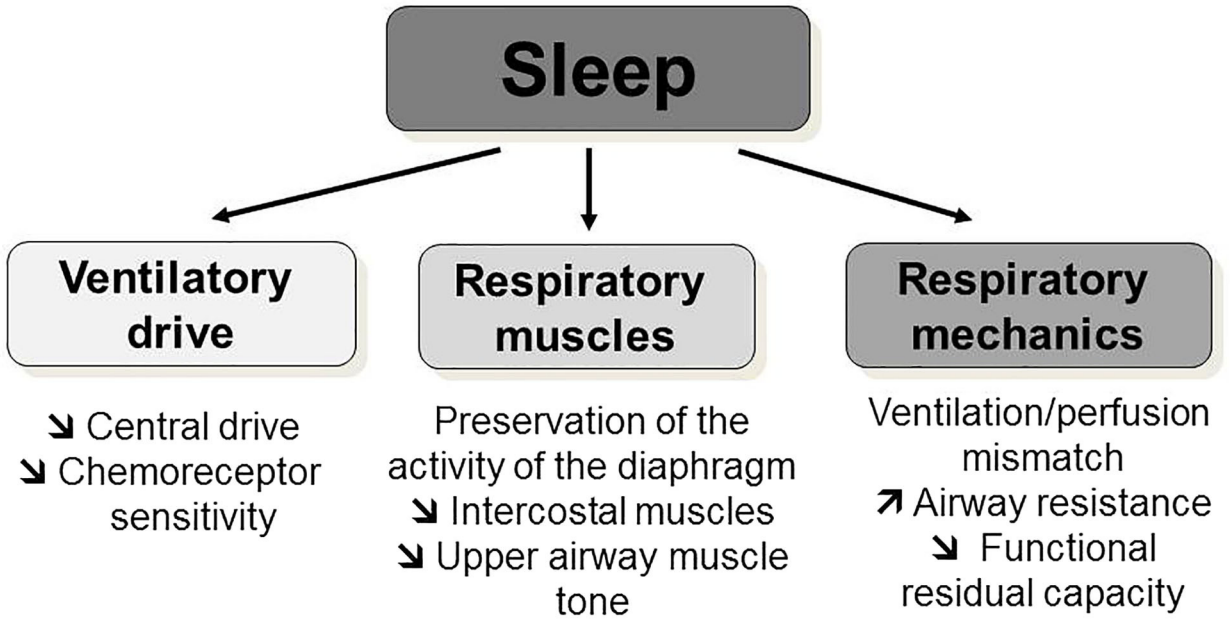

FIGURE 2 | Physiological respiratory changes during sleep. Sleep is associated with physiological changes: a decrease in central drive and chemoreceptor sensitivity; a decrease of the intercostal and the upper airway muscles activity and tone with a preservation of the activity of the diaphragm; and an increase in ventilation–perfusion mismatch, in airflow resistance, and a fall in functional residual capacity.

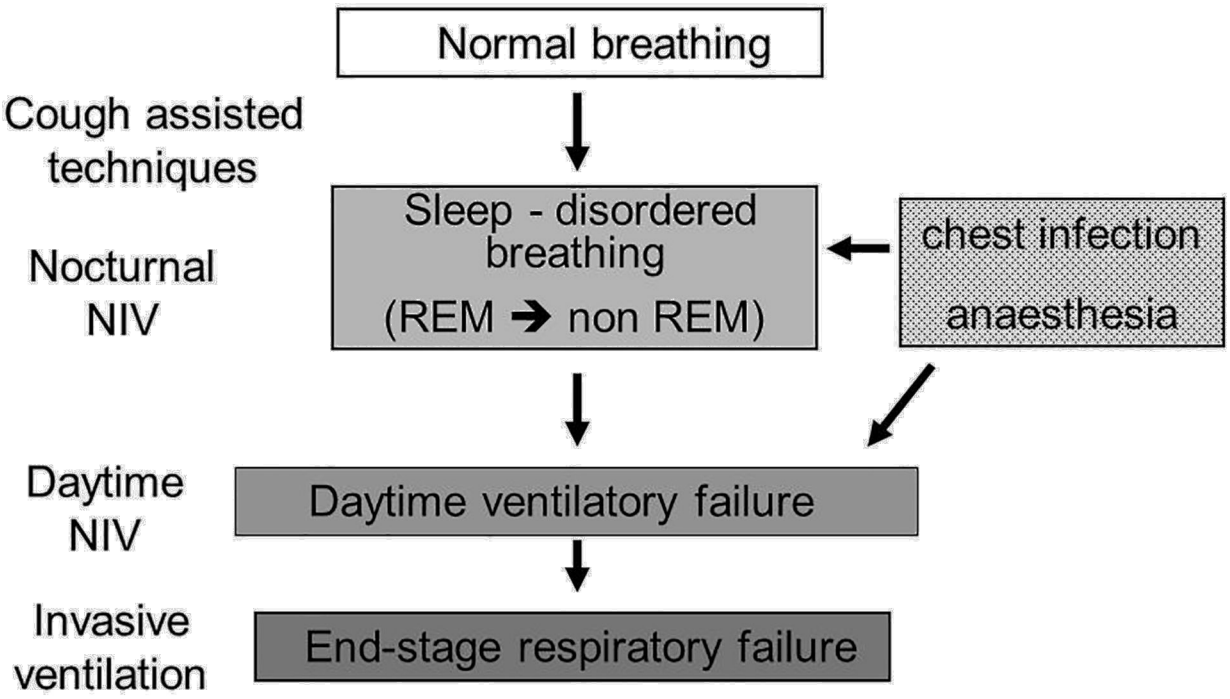

FIGURE 3 | Progression of sleep-disordered breathing toward respiratory failure progressive neuromuscular disorders. Nocturnal hypoventilation during rapid-eye movement sleep is the first breathing abnormality that a patient with neuromuscular diseases may develop during the progression of the weakness of their respiratory muscles. Cough assisted-techniques should be implemented at an early stage, before the onset of nocturnal hypoventilation. Even at an early stage, acute respiratory failure can be precipitated by a respiratory infection or an anesthetic procedure, underlying the importance of preventative measures. With the progression of respiratory muscle weakness, the patient will develop continuous nocturnal and daytime hypoventilation. Daytime ventilation may postpone the discussion of a tracheotomy, which will need to be discussed at the time of end-stage respiratory failure. REM, rapid-eye movement; NIV, non-invasive ventilation.

mainly been identified for patients with DMD who represent a relative homogeneous group of patients. As such, the forced expiratory volume in 1 s (FEV1), daytime PaO_2 and $PaCO_2$, base excess and the rapid shallow breathing index were all significantly correlated to nocturnal hypoventilation in patients with DMD (21). Another study in children with various NMD did not identify a sensitive and specific daytime lung function or respiratory muscle test that was associated with, or predictive of, nocturnal hypoxemia or hypercapnia (22). In clinical practice, it seems important to take into account the type of NMD as nocturnal hypoventilation occurs preferentially in disorders characterized by a prominent diaphragmatic weakness (23). As such children with a COL6 myopathy or a selenopathy should be screened systematically for sleep disordered breathing (8, 9). Prioritized screening is also recommended for infants or young children with congenital myopathies or rapidly progressive NMD (24).

In children with NMD, the documentation of nocturnal hypoventilation by means of a polysomnography is recommended but not mandatory prior to starting NIV because "isolated" abnormal nocturnal gas exchange may be sufficient (25). Indeed, a prospective evaluation of 10 children and adults with a NMD or a thoracic deformity and isolated nocturnal hypercapnia without daytime hypercapnia showed that 9 patients progressed to overt daytime respiratory failure within a period of 2 years (25). However, in the absence of a validated definition of alveolar hypoventilation, different definitions are used in the literature, leading to a different prevalence and severity of alveolar hypoventilation (26). Moreover, the scoring of respiratory events by the American Academy of Sleep Medicine (AASM) is not adapted for patients with NMD (27). Indeed, apneic events are rare in patients with NMD. Progressive simultaneous decrease in airflow and thoracic and abdominal movements, suggestive of global inspiratory muscle weakness, are more common but not scored as respiratory events unless they are accompanied by a (micro)-arousal or a desaturation (28). Paradoxical breathing with opposition phase on the thoracic and abdominal belts may be the consequence of diaphragmatic dysfunction or weakness of the intercostal muscles and should not be falsely scored as an "obstructive event" (28–30). In clinical practice, periods of "reduced ventilation" or paradoxical breathing, more than obstructive and/or central apnea-hypopneas, especially during rapid-eye movement sleep, associated with a pulse oximetry (SpO_2) $< 90\%$ and/or a transcutaneous CO_2 ($PtcCO_2$) value > 50 mmHg are indicative of an insufficient respiratory muscle performance and should discuss the initiation of long term NIV in children with NMD.

In conclusion, screening with at least an overnight gas exchange recording to detect nocturnal hypoxemia and/or hypercapnia, and if possible with a more complete sleep study, should be a priority in all children with any NMD that may be associated with nocturnal hypoventilation. Symptoms of sleep-disordered breathing are insufficiently sensitive and specific and tend to appear late in the course of NMD (17). For the future, the determination of the efficacy of NIV according to the different clinical scenarios and the underlying disease seems important. Larger prospective studies, in homogeneous group of patients with NMD, are also warranted to confirm the benefit of the initiation of NIV at the stage of "isolated" nocturnal hypoventilation.

A pre-operative training with NIV and a cough assisted technique before a planned surgical intervention, such as a spinal fusion, has been shown be very effective to improve the post-operative respiratory outcome and reduce the incidence of respiratory complications in selected children with NMD and cerebral palsy (31).

WHAT ARE THE BENEFITS OF NIV?

The large use of NIV in children with NMD contrasts with the limited number of studies that have evaluated the benefits of NIV in children. Studies involving a small number of patients have shown that NIV is associated with a correction of nocturnal and daytime gas exchange, improved sleep quality, and reduced symptoms associated with sleep-disordered breathing (4–6). NIV has also been associated with an increase in survival in patients with DMD in case series and a nationwide study in Denmark. Indeed, an analysis of the national DMD register in Denmark showed that mortality significantly fell between 1977 and 2001 due to the large increase in ventilator users (32). NIV, associated with nutritional support and cough-assisted techniques, has also been shown to increase survival in infants with SMA type I (33, 34). NIV was also associated with an improvement in the quality of life in infants with SMA and boys with DMD (3, 16, 35, 36).

NIV, associated with mechanical insufflation-exsufflation has been shown to prevent thoracic deformities and consequent thoracic and lung hypoplasia in young children with NMD (37). Intermittent positive pressure breathing (IPPB), which consists in the delivery of intermittent high inspiratory pressures, usually on a daily basis, has been shown to increase ventilation in patients with NMD (38). Both NIV and IPPB technique are also efficient to prevent atelectasis and the risk of pneumonia in children with NMD (39). In clinical practice, NIV is associated with improved feeding, weight gain and growth, which may be related to a decrease of the work of breathing and consequent caloric burn and improved eating and swallowing (6). Neurocognitive dysfunction and behavioral disturbances are the most common and severe consequences of obstructive sleep apnea (OSA) in children (40) but this aspect has been less studied in children with NMD. Patient-reported benefits of mouthpiece ventilation associated a reduction in dyspnea and fatigue as well as an improvement in speech and eating in a study of 30 patients (41).

WHICH NIV EQUIPMENT AND SETTINGS ARE RECOMMENDED?

NIV equipment comprises the interface, the circuit and the device. During NIV, a higher level of positive pressure is delivered during inspiration, by means of a volume- or pressure-targeted mode. The first ventilators used for patients with NMD delivered a volume-targeted ventilation, characterized by the generation of a fixed inspired volume during a given time span. The advantage of this mode is the strict delivery of the preset volume. Its

main disadvantage is that this mode is not able to adjust to the variable requirements of the patient, such as physiological changes in central drive, lung compliance and airway resistance during sleep. Importantly, compensation for unintentional leaks is not always possible with this mode, which exposes the patient to the risk of an insufficient effective inspired volume in the presence of unintentional leaks (42). Consequently, nowadays, the ventilator mode that is the most used is a pressure-targeted mode, eventually with a target inspired volume in order to overcome the limitations of volume-targeted ventilation with a single-limb circuit. During this mode, the ventilator measures or estimates each consecutive expired volume and automatically adjusts inspiratory pressure within a predetermined range to ensure a stable target volume (43).

The settings of NIV have to be individually-adjusted to the patient. In children with NMD, the aim is to deliver a physiological tidal volume of ∼8–10 ml/kg. This can be achieved with low inspiratory pressures in young infants having compliant lungs and chest wall, but higher inspiratory pressures may be necessary in older children, those with scoliosis and/or obesity. Expiratory pressures should be set at the lowest values, as patients with NMD usually do not have airway obstruction. A back up rate close to the physiological breathing rate during sleep is recommended in order to limit the inspiratory triggering of the ventilator by the patient, which can be difficult for a child with weakened respiratory muscles. It has to be noted that continuous positive airway pressure (CPAP) is clearly NOT the treatment of sleep-disordered breathing in patients with NMD. Humidification of the circuit is recommended to improve respiratory comfort and prevent drying of bronchial secretions.

Interfaces for NIV may cover the nose (nasal mask), the nose and the mouth (nasobuccal mask), the face (total face mask) and for daytime use, the mouth only (mouthpiece) (44, 45). Nasal pillows (or prongs or cannulas) are minimal contact interfaces which are available for school-aged children and are very well-tolerated (44). Interfaces can be vented, meaning that they incorporate intentional leaks to be used with a single limb circuit and a preset minimal positive expiratory pressure, and non-vented masks, which can be used with a double limb circuit or a single limb circuit with an expiratory valve, and with or without a positive expiratory pressure. A minimal level of expiratory pressure is mandatory for vented masks, in order to allow the clearing of CO_2 during expiration (46, 47). The choice of the interface is determined 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, ventilator (requiring a vented or non-vented interface), comfort and tolerance of the interface, and the patient's ability to remove the interface by him(her)self. In children requiring NIV during daytime, NIV may be performed with the interface used during sleep but also a mouthpiece (12, 41, 48). The advantages, disadvantages and side effects of the different interfaces are listed in **Table 1**.

NIV should be performed with a life support ventilator appropriate for the child's weight, with adequate alarms, and an integrated (± additional) battery. Humidification is recommended to improve respiratory comfort and prevent drying of bronchial secretions. NIV has to be associated with an efficient clearance of bronchial secretions by either, a specific program on the ventilator, IPPB, or mechanical insufflation-exsufflation. The patient and his caregivers should be trained to these clearance techniques in order to prevent or limit bronchial encumbrance and respiratory exacerbations.

TABLE 1 | Advantages, disadvantages and side effects of interfaces for children.

Interface	Advantages	Disadvantages	Side effects
Nasal mask	Small internal volume Large choice	Not usable in case of mouth leaks	Pressure sores, eye irritation if leaks, maxillary retrusion
Nasobuccal mask	Prevents mouth leaks	Large volume, risk of inhalation of gastric content in case of oesogastric reflux, no model available for infants	Pressure sores, eye irritation if leaks, facial deformity
Total face mask	Prevents mouth leaks	Large volume, risk of inhalation of gastric content in case of oesogastric reflux	Pressure sores, facial deformity
Nasal prongs	Small, light No pressure sores	Not usable in case of mouth leaks, no model available for infants	Nasal irritation
Mouthpiece	Small and light, no pressure sores, to be used on demand	Not usable during sleep	None

HOW SHOULD CHILDREN WITH NIV BE FOLLOWED?

NIV is a technically challenging treatment which aim is to be performed at home. NIV is usually initiated in the hospital during a short hospitalization of 2 or 3 nights in order to progressively acclimatize the patient to his (her) NIV treatment. As NIV will be administered during sleep, an overnight monitoring of sleep with the optimal setting(s), at least with an assessment of overnight gas exchange, and ideally with polygraphy or polysomnography, is recommended before discharge. This sleep study can be postponed until the patient is well-adapted to NIV and is able to sleep at least 6 h with his device. Training of the caregivers and of the patient is essential. The caregivers must be familiar with the putting on and taking off of the NIV interface and device and should have an appropriate training on the different problems that may occur at home (49). Careful checking of the caregiver competencies before discharge is mandatory. In order to cope with the shortage of hospital beds and the demands of the families, it is possible to started NIV in an out-setting in selected patients with an efficacy and compliance comparable to an in-hospital initiation (13, 50, 51). Home visits by trained nurses and/or technicians are possible in some countries and constitutes a major factor of the success of a home NIV program. Indeed, compliance with NIV is a major issue as treatment efficiency is related to the length of nocturnal use (52). Most studies have reported relatively low compliance rates

with mean night uses between 3 and 5 h (52–54). However, objective compliance levels close to the recommended sleep duration in children can be achieved by expert centers having a specific NIV therapeutic education program (55). The 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 (49).

There are no validated guidelines for the monitoring or long term follow up of children with NIV. The timing of the follow up visits depends on the age and the medical condition of the child. Our practice consists in a sleep study 1 month after the initiation, and then every 2–6 months, with at least 2 check-ups per year including a full sleep study with NIV. Overnight SpO_2 with $PtcCO_2$ recording during NIV is recommended at each visit as numerous asymptomatic patients remain hypercapnic during sleep with NIV despite a normal overnight SpO_2 and normal daytime blood gases (56). This residual nocturnal hypercapnia can be easily corrected by simple measures such as changing the interface or the ventilator settings (56). Check-ups can also be performed at home with adequate training of staff (57). The 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 residual respiratory events, which is particularly useful for centers which have a limited access to sleep studies (58, 59).

WHAT ARE THE SIDE EFFECTS AND LIMITATIONS OF NIV?

NIV may be associated with side effects. The most common are those caused by the interface and comprise skin injury due to pressure sores, eye irritation due to unintentional air leaks, and facial deformity in young children (60). Skin injury is less common due to the improvements in interfaces for children and the use of "minimal-contact" interfaces such as nasal pillows. Mouth leaks may be minimized by the use of a pacifier in infants, or the change for a nasobuccal mask. Facial flattening and maxillary retrusion are the major side effects in young children and may add an obstructive component to the child's restrictive lung disease (60). These facial deformations may be prevented by the use of nasal pillows or minimized by alternating different interfaces such as a nasal and a nasobuccal mask. Other side effects are less common and may be caused by the positive pressure. Aerophagia, gastric distension, and oeso-gastric reflux may be observed with high inspiratory pressures or in case of patient-ventilator asynchrony. These abdominal side effects may be managed by decreasing the airway pressures, and/or correcting patient-ventilator asynchrony, and/or the use of an abdominal girdle. Unintentional leaks may be associated with discomfort, poor NIV tolerance and poor sleep quality with arousals (61).

In children requiring NIV during daytime, mouthpiece ventilation may be impossible in young children and difficult to accept in older children. Even if NIV is very effective, it may be difficult to apply "around the clock" on a long term basis. Some expert teams have a successful experience with NIV in totally ventilator-dependent children with NMD (33), but others consider that the child should be able to breathe spontaneously without NIV for a minimal time per day in order to be able to be safely maintained at home. A tracheostomy represents a possible option for children with a progressive NMD that has to be prepared and discussed thoroughly with the child and his parents. Within this context, determining the best interests of a child has been described as "balancing benefit 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" (62). In some children and their families, the transition from NIV to a tracheostomy may be associated with a too high burden with regard to the improvement in quality of life of the child and his family (63). NIV may then be used as a part of a palliative care approach, without prolonging excessively a poor or unbearable quality of life. However, this remains a complex and evolving area of health-related quality of life (64–67). Of note, a tracheostomy was not always associated with a decrease in quality of life as evaluated by the patients themselves (68).

CONCLUSION

Long term NIV is an extremely efficacious type of non-invasive respiratory support which has transformed the scope of chronic respiratory failure and severe sleep-disordered breathing in children with NMD by avoiding tracheotomies and allowing the child to live at home with a good quality of life for the child and his family. The tremendous heterogeneity of the disorders, ages, prognosis and outcomes of the patients underlines the necessity of a management by experienced, multidisciplinary pediatric centers, having technical competencies in pediatric NIV, and an expertise in sleep studies and therapeutic education.

AUTHOR CONTRIBUTIONS

BF was the main author of the manuscript. AA, SK, LG, AL, and TT contributed to the management of the children with neuromuscular disease followed in our center and the writing of the manuscript. All authors approved the final version of the manuscript.

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REVIEW
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Long Term Non-invasive Ventilation in Children With Central Hypoventilation

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Central hypoventilation (CH) is a quite rare disorder caused by some congenital or acquired conditions. It is featured by increased arterial concentration of serum carbon dioxide related to an impairment of respiratory drive. Patients affected by CH need to be treated by mechanical ventilation in order to achieve appropriate ventilation and oxygenation both in sleep and wakefulness. In fact, in severe form of Congenital Central Hypoventilation Syndrome (CCHS) hypercarbia can be present even during the day. Positive pressure ventilation via tracheostomy is the first therapeutic option in this clinical condition, especially in congenital forms. Non-Invasive ventilation is a an option that must be reserved for more stable clinical situations and that requires careful monitoring over time.

Keywords: central hypoventilation, arterial concentration of serum carbon dioxide, central apnea, non-invasive ventilation, children

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INTRODUCTION

Central hypoventilation (CH) is a quite rare disorder caused by some congenital or acquired conditions. It is featured by increased arterial concentration of serum carbon dioxide ($PaCO_2$) related to an impairment in respiratory drive (1). Diagnosis is not easy to do, as hypoventilation occurs mainly during sleep, but it must be made as early as possible, as hypoventilation can give serious long-term complications.

PATHOPHYSIOLOGY

Hypoventilation refers to an increased $PaCO_2$ due to inadequate gas exchange. This concept is summarized in the equation $PaCO_2 = K \times VCO_2/VA$ where K is a constant. It reads like this: $PaCO_2$ is directly proportional to the body's CO_2 production (VCO_2) and inversely proportional to alveolar ventilation (VA). In other words, $PaCO_2$ increases when CO_2 production increases or alveolar ventilation decreases.

The breathing system is regulated by a set of receptors sensitive to changes in partial pressure of oxygen (PaO_2), $PaCO_2$ and hydrogen potential (pH), as well as other factors, such as the stretching of bronchial smooth muscle cells. Central chemoreceptors, located bilaterally below the ventro-lateral surface of the bulb, respond to small changes in $PaCO_2$. Peripheral chemoreceptors are located in structures called glomas, which are located at the bifurcation of the common carotid artery (carotid glomas), and at the aortic arch (aortic glomas) and are sensitive to changes in PaO_2, $PaCO_2$ and pH (2, 3).

In healthy subjects, $PaCO_2$ is the main ventilation stimulating factor. If $PaCO_2$ increases, ventilation initially increases with a corresponding greater tidal volume, followed by an increase in respiratory rate. In case of hypoxia, ventilation initially increases but then decreases over time (4).

During sleep, the resistance of the upper airways increases, muscle tone decreases (in non-REM sleep) until it is completely abolished in sleep with rapid eye movement (REM), when breathing is maintained by the diaphragm only. During non-REM sleep, ventilation decreases and causes a slight increase in $PaCO_2$ and a decrease in PaO_2 compared to wakefulness. In the REM phase, breathing is superficial and irregular and the respiratory response of the respiratory centers to O_2 and CO_2 is reduced (5, 6).

CLINICAL ASPECTS

CH can be due to congenital or acquired conditions and the onset of symptoms can occur at different times depending on the underlying pathology. It's hard to find specific signs or symptoms diagnostic of central sleep apnea (CSA) and even more of hypoventilation, so clinicians must be aware that this pathway can occur in the following diseases.

Congenital central hypoventilation syndrome (CCHS), also known as Ondine's curse, is a rare condition that causes primary alveolar hypoventilation, firstly described in 1970 (7). In 2003 Amiel and collaborators (8) discovered the gene responsible of the disease, which is the paired-like homeobox 2B (PHOX2B), located on chromosome 4p12. This gene is a transcription factor which plays a central role in the differentiation of the neural lineage of autonomic nervous system. Most mutations occur de novo in CCHS patients, but inheritance can derive by parents with an autosomic dominant pattern with incomplete penetrance or with a mosaicism. Majority (90%) of patients with this congenital condition have a polyalanine expansion mutations (PARMs) in exon 3 (9). Other patients present nonsense, missense, frameshift or stop codon mutations in exon 1, 2, and 3, defined as non-polyalanine expansion mutations (NPARMs) (10). Over time, knowledge of the gene let us understand that PHOX2B mutation determines the phenotype of the patients (11, 12) and must guide care choices.

Patients with CCSH often present apnea and cyanosis in neonatal period, edema and signs of right heart failure associated with pulmonary hypertension, tachycardia and sweating during sleep, early breath holding spells, episodes of unexplained convulsions, severe Apparent Life-Threatening Events (13).

CCHS is also related to some tumors of neural crest origin (ganglioneuroma, neuroblastoma, ganglioneuroblastoma), or symptoms attributed to abnormal development of neural crest cells such as the following manifestations: ophtalmologic (anisocoria, strabismus), cardiovascular (alterations of cardiac rhythm or blood pressure disregulation), endocrinologic (hyperinsulinism, hypoglycemia, hyperglycemia), gastrointestinal (constipation, Hirschprung's disease) (14).

Pathophysiology of hypoventilation in CCHS is not clear yet. Breathing and autonomic dysregulation can be related to alterations of the brain, showed by functional or structural MRI, but it is not well understood if they can be determined in neurogenesis consequent to genetic mutations or secondary to hypoxic, hypercarbic, or perfusion damage (15). Moreover there are multiple impaired processes which can be causative factors in the onset of respiratory symptoms.

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) is a rare disorder presenting in childhood with rapid weight gain, hypothalamic endocrine dysfunction, and severe hypoventilation. Clinical features include ophthalmologic abnormalities, altered thermoregulation, gastrointestinal dysmotility, behavior disorders, altered pain perception and tumor of neural crest origin (16). Respiratory phenotype of ROHHAD may initially present with OSA and only develop central hypoventilation later (17). Despite many clinical aspects in common with CCHS, mutations of PHOX2B are lacking in ROHHAD patients (18). A recent paper support the hypothesis of a possible aberrant immune process in pathogenesis of the disease (19).

Prader-Willi syndrome (PWS) is a genetic disorder due to loss of function of specific genes in chromosome 15. It is characterized by poor muscle tone often associated to feeding problems during infancy; in childhood an insatiable appetite often leads to obesity; patients are typically affected by mild to moderate intellectual impairment, behavioral problems, short stature, hypogonadism with genital hypoplasia, incomplete pubertal development (20).

PWS patients present impairments in ventilatory control: absent or altered hypoxic ventilatory response, reduced hypercapnic ventilatory response in obese subjects, altered pulmonary mechanics due to hypotonia, respiratory muscle weakness, kyphoscoliosis, and obesity. The phenotype of sleep disordered breathing evolves over time from a central pattern in infants to an obstructive one in older children and often hesitates in excessive daytime sleepiness (21). Long-term treatment with growth hormone is indicated for children with PWS but it may determine worsening of sleep-disordered breathing soon after the initiation; therefore an evaluation by polysomnography within the first 3–6 months of starting therapy should be repeated (22).

Other congenital diseases, as Familial dysautonomia (23), Arnold Chiari malformations (24), achondroplasia (25), disorders affecting mitochondrial metabolism (26) may result in central hypoventilation, within a wider spectrum of sleep disordered breathing. These patients must be investigated as well as the increasing population with **acquired central hypoventilation** which is constituted by those previously healthy children presenting damage of respiratory centers in the brain. Gangliogliomas and consequences from neurosurgical procedures were found mostly represented (27), but central nervous system infections, encephalitis, trauma, and other central nervous system tumors can be other onset reasons.

DIAGNOSIS

Hypoventilation is caused by insufficient alveolar ventilation which causes altered blood gas values. American Academy of Sleep Medicine (AASM) (28, 29) scored hypoventilation during sleep when >25% of the total sleep time as measured by either the arterial PCO_2 or surrogate is spent with a $PCO_2 > 50$ mmHg. The process of arterial blood is the gold standard method to diagnose hypoventilation but its use during sleep is difficult and normally not available in a sleep laboratory. Therefore, AASM stated that an elevated $PaCO_2$ obtained immediately after waking allows diagnosis of hypoventilation during sleep. So, surrogate measures such as transcutaneous PCO_2 ($PtcCO_2$) and end-tidal PCO_2 ($PETCO_2$) are commonly used and considered acceptable methods for assessing pediatric alveolar hypoventilation.

$PtcCO_2$ has a good correlation with $PaCO_2$, but its response time to acute changes in ventilation is longer than the $PETCO_2$. The American Association for Respiratory Care Clinical Practice Guidelines (30) recommend that arterial blood gas values be compared to transcutaneous readings, in order to verify them in acute situations. $PtcCO_2$ is a very useful device in order to monitor the adequacy of ventilation (31).

Monitoring of exhaled CO_2 (capnography) is very used in children, but it is not accurate with low tidal volume and fast respiratory rates, as in infants or in acute distress, because a defined plateau in expiratory curve is not available. Usually $PaCO_2$ is higher of $PETCO_2$ between 2 and 7 mmHg (28). End-tidal PCO_2 monitoring cannot be used during application of supplemental oxygen or during mask ventilation because exhaled gas sample is diluted and in case of mouth breathing.

Polysomnography is the gold standard to score central, obstructive or mixed events. Usually apneas recur during REM sleep, but in CCHS the events occur during NREM one. Central apnea is defined by cessation of airflow without respiratory effort and duration of 20 s or longer, or duration of two breaths during baseline breathing and association with an arousal or ≥3% oxygen desaturation, or, for infants younger than 1 year of age, duration of two breaths during baseline breathing and association with a decrease in heart rate to <50 beats per minute for at least 5 s or <60 beats per minute for 15 s (29).

MANAGEMENT

Clinicians must be aware of the different therapeutic options and be able to choose the correct one, even because the amount of ventilator assistance required in these syndromes is extremely variable.

Ventilation

In patients requiring continuous ventilation, positive-pressure ventilation via tracheostomy is the most common and effective method of treatment (1). American Thoracic Society statement still advice this ventilation option in the first years of life for CCHS patients (13) since ventilator system becomes more stable with age.

If possible, tracheostomy tube should be cuffless and smaller than airways dimension, in order to reduce the risk of tracheomalacia and to consent the utilization of speaking-valve when patient is not ventilated.

Non-invasive positive-pressure ventilation (NPPV) provides adequate ventilation through a mask; this modality can be chosen in patients requiring ventilation only during sleep. Its major benefit is the avoidance of tracheostomy and its complications. Nasal masks are the most used, as in all populations that perform long-term ventilation. Bilevel positive airway pressure (BiPAP) ventilation mode is the most used as it provides variable continuous flow, with fixed inspiratory and expiratory positive airway pressure whose difference is proportional to tidal volume. As children with central hypoventilation syndromes don't trigger the ventilator adequately during sleep, the timed mode with a set respiratory rate is to be preferred.

Recently intelligent volume-assured pressure support (iVAPS), which can modulate pressure support to ensure constant alveolar ventilation (32) has been proponed for CCHS patients. The rationale for the proposal is that, since these patients have variable ventilation between REM and NREM sleep, pressure is automatically modulated to better control carbon dioxide levels throughout the night (33). Some manufacturers indicate that iVAPS is FDA cleared for patients weighing more than 66 lb (>30 kg). A 10 months old CCHS infant report shows that, in case of availability of an adequate nasal mask, of a correct education of the parents and of a mid-face hypoplasia prevention program, it is possible to use NIV in AVAPS mode (average volume assured pressure support), which it is similar to iVAPS, even in younger children. This ensures less oscillation of the $PaCO_2$ values during sleep (34).

Mid-face hypoplasia is a frequent complication of mask ventilation, especially if introduced in infancy. Provide two different masks with different points of pressure on the face is a good strategy, but also a closely follow up by pediatric maxillofacial surgeon and orthodontist should be performed.

An increasing number of children with CCHS have been successfully transitioned from invasive ventilation to BiPAP ventilation and recently a proposal of an algorithm for decannulation was published (35). By the moment there are not specific indications about optimal time to switch from tracheostomy to NPPV because it is a choice closely linked to the patient and his family, but ending the decannulation program before adolescence can be a good option.

Negative-pressure ventilation (NPV) causes inspiration as it creates a negative inspiratory pressure around the chest of the patient, using a bell of his appropriate size.

A small group of CCHS children passed from invasive ventilation to negative pressure ventilation removing tracheostomy (36) but its use is really limited because of non-portability, obliged supine position during sleep, skin irritation, uncomfort, risk of obstructive sleep apneas relied to asynchrony between vocal cords opening and thoracic inspiratory efforts (1).

In patients with central hypoventilation syndromes, a second ventilator in the home is necessary, in the event of technical failure. Moreover, if ventilation is continuous, a power generator or a continuous energy supply according with local energy company must be available.

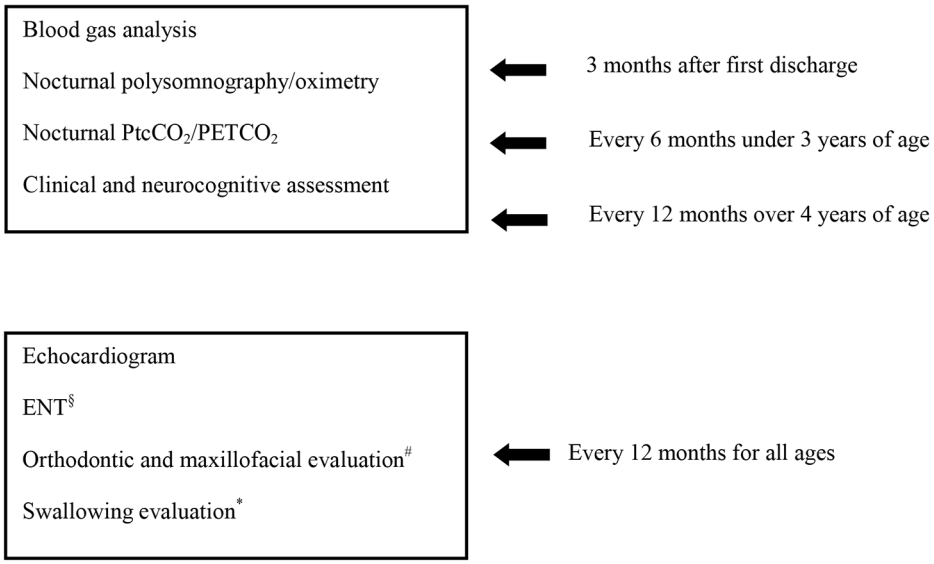

FIGURE 1 | Follow up program for clinically stable patients with central hypoventilation. §In case of tracheostomy. #In case of NIV, after 3 years of age. *Evaluation carried out as needed.

Diaphragm Pacing

Diaphragm pacing can generate breathing using the child's own diaphragmatic contraction by the electrical stimulation of the phrenic nerve (37). This device is very useful in patients with central hypoventilation syndrome requiring ventilator support 24 h a day. Contrary to adults, in children ventilation is still necessary as diaphragm needs a rest some hours a day but, moreover, because complete airway obstruction after pacing implantation is described as upper airway muscle contraction is not synchronous with paced inspiration (38).

These patients require careful and structured management over time. In **Figure 1** we suggested the tests to be performed over time for central hypoventilation.

Obviously, the pathologies underlying hypoventilation will require specific follow up for the disease and its complications.

Last but not least, the follow up must be individualized on the basis of the specific characteristics of the patient, with a prompt response in the event of exacerbations or clinical worsening.

CONCLUSION

Central hypoventilation syndrome is the clinical manifestation of a heterogeneous group of pathologies. Therefore, clinician must adequately treat respiratory impairment, but also other aspects related to primary disease with a multidisciplinary approach.

Ventilation must be suited individually, basing on clinical pathway, on the amount of daily time spent in ventilation, on patient and family decision, if possible. Non-invasive ventilation has multiple advantages, but it requires a considerable effort and needs a careful monitoring over time.

AUTHOR CONTRIBUTIONS

MP designed the review in collaboration with IE. MG and ER contributed to the content. EB and RC revised the content of review.

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REVIEW
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Non-invasive Ventilation for Children With Chronic Lung Disease

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Advances in medical care and supportive care options have contributed to the survival of children with complex disorders, including children with chronic lung disease. By delivering a positive pressure or a volume during the patient's inspiration, NIV is able to reverse nocturnal alveolar hypoventilation in patients who experience hypoventilation during sleep, such as patients with chronic lung disease. Bronchopulmonary dysplasia (BPD) is a common complication of prematurity, and despite significant advances in neonatal care over recent decades its incidence has not diminished. Most affected infants have mild disease and require a short period of oxygen supplementation or respiratory support. However, severely affected infants can become dependent on positive pressure support for a prolonged period. In case of established severe BPD, respiratory support with non-invasive or invasive positive pressure ventilation is required. Patients with cystic fibrosis (CF) and advanced lung disease develop hypoxaemia and hypercapnia during sleep and hypoventilation during sleep usually predates daytime hypercapnia. Hypoxaemia and hypercapnia indicates poor prognosis and prompts referral for lung transplantation. The prevention of respiratory failure during sleep in CF may prolong survival. Long-term oxygen therapy has not been shown to improve survival in people with CF. A Cochrane review on the use NIV in CF concluded that NIV in combination with oxygen therapy improves gas exchange during sleep to a greater extent than oxygen therapy alone in people with moderate to severe CF lung disease. Uncontrolled, non-randomized studies suggest survival benefit with NIV in addition to being an effective bridge to transplantation. Complications of NIV relate mainly to prolonged use of a face or nasal mask which can lead to skin trauma, and neurodevelopmental delay by acting as a physical barrier to social interaction. Another associated risk is pulmonary aspiration caused by vomiting whilst wearing a face mask. Adherence to NIV is one of the major barriers to treatment in children. This article will review the current evidence for indications, adverse effects and long term follow up including adherence to NIV in children with chronic lung disease.

Keywords: children, chronic lung disease in childhood, Non-invasive Ventilation (NIV), cystic fibrosis, Bronchopulmonary Dysplasia (BPD)

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INTRODUCTION

Non-invasive ventilation (NIV) is the application of ventilatory support via a non-invasive interface instead of an endotracheal tube or tracheostomy. Following early mechanical ventilation applications as negative pressure ventilation in the 1930s, the use of NIV in children has increased exponentially around the world in recent years (1–3). There are many studies showing the benefits and superiority of NIV in comparison with invasive ventilation via tracheostomy in terms of quality of life, health care costs, and morbidity (4, 5).

There are two main modes to provide positive airway pressure support. Continuous positive airway pressure (CPAP) provides constant positive pressure throughout the entire respiratory cycle, which prevents airway closure. Therefore, CPAP does not assist spontaneous inspiration of the patient, CPAP improves gas exchange and oxygenation by increasing functional residual capacity (FRC). Bilevel positive airway pressure (BIPAP) delivers a pre-set positive pressure at inspiration as well as a background positive expiratory pressure. BIPAP improves ventilation and gas exchange more effectively than CPAP alone by increasing tidal volume as well as FRC (6).

Normal spontaneous ventilation requires a balance between neurologic mechanism controlling ventilation (respiratory drive) together with respiratory muscle power and respiratory load. Conditions that disrupt this respiratory balance are the main indications for NIV such as upper airway obstructions, lower airway obstructions due to chronic lung disease, weakness of respiratory muscles and disorders of central drive (4).

Advances in medical care and expansion of supportive care options have contributed to the survival of children with complex disorders including children with chronic lung disease (CLD). Asthma, bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), non-CF bronchiectasis, bronchiolitis obliterans (BO), interstitial lung disease (ILD) and CLD in children with HIV cause airway and parenchymal inflammation, decreased lung compliance leading to chronic airflow obstruction, tachypnea and increased work of breathing. When the respiratory load increases, the work of the respiratory muscles also increases to avoid respiratory failure. This causes shortness of breath, exercise intolerance, growth failure and if ventilatory support is inadequate, it can be associated with hypoxemia and hypercapnia leading to pulmonary hypertension, cor pulmonale, and right heart failure. NIV is not needed for all CLD as in the case of asthma vast majority of patients do not need NIV.

In obstructive lung diseases such as CF, airflow obstruction, and parenchymal lung damage cause increased pulmonary resistance and decreased compliance due to parenchymal fibrotic change resulting in increased respiratory load. Respiratory muscle weakness caused by malnutrition and chronic pulmonary hyperinflation may also contribute to impaired respiratory function (7).

The respiratory load is increased in ILD due to several mechanisms. Children with ILD typically have a rapid shallow breathing pattern as a result of an increase in central drive, due to vagally mediated response to decreased lung compliance. Lung compliance is decreased in children with ILD as a result of extracellular matrix deposition. In addition, increased lung resistance and work of breathing result in increased respiratory rate. An impairment in gas exchange due to ventilation-perfusion mismatch and reduced diffusion capacity also contribute to the increase in respiratory rate and respiratory load (8, 9).

NIV is not a universal requirement for patients with chronic lung disease. The primary aims of NIV in children with CLD are to improve minute ventilation, increase alveolar recruitment and improve compliance which in turn unload respiratory muscles and reduce work of breathing (4). Non-invasive ventilation is also an effective treatment for nocturnal hypoventilation. By delivering a positive pressure during patient's inspiration, NIV is able to reverse nocturnal alveolar hypoventilation in patients who experience hypoventilation during sleep, such as patients with chronic lung disease (2, 3). Several physiologic mechanisms are responsible for hypoventilation during sleep. Compared to wakefulness, there is a decrease in central drive and chemoreceptor sensitivity affecting ventilatory response to hypoxia and hypercapnia during sleep. Sleep has also adverse effects on respiratory muscle function. While the function of the diaphragm is preserved, there is a decrease in the tone of the accessory respiratory muscles. Additionally, decreased FRC, increased ventilation-perfusion mismatch, increased airflow resistance also play a role in the development of nocturnal hypoventilation (10). Children with moderate-severe CF lung disease have lower oxygen saturations and more frequent desaturation episodes during sleep compared to healthy children, due to adverse effects of sleep on the existing ventilation-perfusion mismatch caused by parenchymal lung disease. This decline in oxygen saturation levels is correlated with awake resting oxygen saturation, and disease severity such as FEV_1 % predicted. Poor sleep quality, reduced sleep efficiency, and total sleep duration among children with CF also contribute to nocturnal hypoxemia in these children (11).

Furthermore, in BPD, central apneas and abnormal ventilatory responses to hypoxic and hypercarbic states due to the immaturity of respiratory drive and sleep fragmentation are common. In addition to the immaturity of respiratory drive, upper airway obstruction is also increased during sleep as a result of a smaller caliber upper airway and increased compliance of the chest wall (12, 13).

As mentioned above, there are also various changes in respiratory physiology in ILD. During sleep, decreased respiratory drive, chemosensitivity and decreased activity of respiratory muscles including the diaphragm cannot maintain alveolar ventilation. Decreased lung volumes and altered ventilation-perfusion match further increase alveolar hypoventilation in ILD (14, 15).

The use of NIV in CLD may rarely be contraindicated, ineffective, or in some cases harmful. The presence of pneumothorax in children with advanced disease is an absolute contraindication for NIV. Judicial evaluation of patients with severe cystic/cavitatic lung disease and their suitability for NIV is required. Besides, in cases with treatment failure, nasal polyps should be considered in children with CF and asthma (10). In patients with ILD, who have a low percentage of the recruitable lung, high PEEP levels may be ineffective or even

harmful as a result of hyperinflation of already open lung regions (16, 17).

This article will review the current evidence for indications, adverse effects and long term follow up including adherence to NIV in children with chronic lung disease.

ASTHMA

Asthma is a common chronic lung disease, characterized by chronic airway inflammation, persistent remodeling of the small airways and bronchial hyperresponsiveness. The main clinical findings are wheezing, shortness of breath, chest tightness and cough with variable expiratory airflow limitation. Regular controller therapy is required to achieve symptom control and avoid respiratory morbidity such as exacerbations (18, 19).

Asthma exacerbation occurs due to reversible, diffuse lower-airway obstruction, caused by airway inflammation and edema, smooth muscle contraction, and mucus hypersecretion. This obstruction of the lumen limits airflow and causes premature closure of the airways (20). An active expiration by continuous activation of inspiratory muscles is required to empty the lungs. Besides, increased airway resistance and air trapping make it difficult to further stretch the hyperinflated lungs for adequate inspiration. Progressive air trapping increases positive end-expiratory pressure (PEEP), also known as auto-PEEP or intrinsic PEEP. This increase is correlated with the degree of the obstruction, and results in muscle fatigue and respiratory failure, if not properly and promptly treated (21). The main initial therapies include bronchodilators, corticosteroids and oxygen supplementation. Despite improvements in the management of asthma exacerbations, some patients experience severe exacerbations not responding optimally to medical therapies (18).

NIV may be able to counteract the intrinsic PEEP by delivering an extrinsic EPAP. It maintains airway patency, which results in improvement of airflow, re-expansion of atelectatic lung segments, and a decrease in respiratory muscle load. These changes also improve ventilation–perfusion mismatch. Also, NIV can increase tidal volume by improving respiratory muscle functions (22–24).

Delivering nebulized bronchodilators via NIV also improves lung aerosol dispersion, and may increase response to bronchodilators, which may improve clinical outcomes (25, 26).

Based on this physiologic rationale, there are several studies on the NIV use for children with acute asthma exacerbations. A recent Cochrane review included the following two studies on the use of NIV in children with acute asthma exacerbation (19). Thill et al. studied the effect of NIV among 20 children with acute asthma exacerbation who were admitted to the pediatric intensive care unit (ICU) in a prospective cross-over study. Patients were randomized to receive either 2 h of NIV followed by crossover to 2 h of conventional therapy or 2 h conventional therapy followed by 2 h of NIV. NIV was associated with a decrease in respiratory rate for all patients. There was also a decrease in clinical asthma scores both in total and in each of the sub-scores. Additionally, the discontinuation of NIV was associated with an increase in respiratory rate and clinical asthma score. No adverse events related to NIV were observed during the study. Authors demonstrated that NIV improved clinic findings of respiratory distress and it may be a treatment option for the children with severe acute lower airway obstruction refractory to medical therapy (23).

The effect of early initiation of NIV in asthmatic children admitted to the ICU was investigated in a randomized controlled study by Basnet et al. NIV use for 24 h as initial treatment was compared to standard medical treatment alone. This study revealed that the improvement in clinical asthma score and respiratory functions determined by a decrease in respiratory rate and oxygen requirements were greater in the NIV group. There was also a trend to a decrease in the need for other adjunct therapies. Non-invasive ventilation was well-tolerated except for one patient (27).

Despite increased use of NIV, the evidence on the role of NIV among asthmatic patients is weak (18, 19). A study investigated outcomes of asthmatic patients admitted to the ICU revealed that the NIV use increased from 11 to 39% over 12 years. However, intubation rates remained similar despite increasing rates of NIV use (28).

The use of NIV in asthmatic patients may be considered as an add-on therapy to standard care. If NIV is tried, close monitoring of the patient is essential. Global Initiative for Asthma (GINA) recommends that NIV should not be attempted in agitated patients with asthma, and patients should not be sedated in order to receive NIV (Evidence D) (18).

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia is the most common cause of chronic lung disease in infancy and the most common morbidity of prematurity (29). Since the first definition of the BPD, the definition is evolved over time (30). According to a workshop report, BPD is defined as oxygen need for 28 days and an assessment of respiratory support at 36 weeks' postmenstrual age was proposed for defining the severity (**Table 1**) (31). There is a further definition to determine the severity of the disease. Infants in room air at 36 weeks PMA are "mild," those requiring <30% oxygen are "moderate," and those requiring ≥30% oxygen or positive pressure ventilation are "severe" (32, 33). Bronchopulmonary dysplasia is also divided into early, evolving and established BPD. The time from birth to the 1st week of life indicates early BPD. The period between 1st week of life and 1st month of life called as evolving BPD and established BPD is considered to occur after 1st month of life (34). The current definitions of BPD still have some limitations such as the optimal timing to assessment (35). A study evaluating optimal definition of BPD to predict long-term respiratory outcomes at 18–21 months corrected age showed receiving oxygen and/or respiratory positive-pressure support at 40 weeks' PMA was most strongly associated with serious respiratory outcome among those at each of 34–44 weeks' PMA (36).

Despite significant advances in neonatal care over the recent decades, the incidence of BPD has not diminished. The reported

TABLE 1 | Definition of BPD: Diagnostic criteria.

Gestataional age	<32 week	≥32 week
Time point of assessment	36 week PMA or discharge to home, whichever comes first	>28 day but <56 day postnatal age or discharge to home, whichever comes first
Treatment with oxygen >21% for at least 28 d plus		
Mild	Breathing room air at 36 week PMA or discharge, whichever comes first	Breathing room air by 56 day postnatal age or discharge, whichever comes first
Moderate	Need for <30% at 36 week PMA or discharge, whichever comes first	Need for <30% at 56 day postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 week PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 day postnatal age or discharge, whichever comes first

BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; NIH, National Institutes of Health; PMA, postmenstrual age; PPV, positive pressure ventilation. Source: Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(07):1723–1729.

rate varies between 30 and 59% depending on the gestational age; babies who are <1,000 g, and <28 weeks of gestation, accounting for most of the cases (32). Most affected infants have mild disease and require a short period of oxygen supplementation or respiratory support. However, severely affected infants can become dependent on positive pressure support for a prolonged period. The severity of BPD is also inversely correlated with gestational age. The incidence of severe BPD is reported as 16 and 25% in infants born <32 and <27 weeks, respectively, with a male predominance. Although the main predisposing factor is prematurity, many other factors such as antenatal inflammation, intrauterine growth retardation, maternal smoking, male gender and genetic factors are associated with the increased risk of BPD and poor respiratory outcomes (37).

Pulmonary inflammation, oxidative stress, mechanical trauma to the immature lungs cause disrupted alveolar and vascular growth leading to fewer and larger alveoli, decreased pulmonary vasculature, and variable smooth muscle proliferation (38, 39). These changes generate respiratory morbidity and long-term impairment in lung functions in BPD survivors. Preterm infants with BPD experience more wheeze episodes, require inhaled medications more frequently and hospitalizations during the 1st years of life (40, 41). As infants with BPD grow, there is a decrease in total pulmonary resistance, an increase in pulmonary compliance, and an improvement in the ventilation-perfusion ratio, resulting in decreased respiratory rate, increased tidal volume, and improved oxygenation (42). However, cross-sectional and longitudinal studies evaluating respiratory functions following the development of the BPD revealed a significant airway obstruction from the infancy tracking into adulthood (43–46). These results support that BPD survivors may not achieve their optimal airway growth.

There is no single management strategy for the wide spectrum of clinical presentations of BPD and care must be individualized. Gentle respiratory support, titration of supplemental oxygen are mainstay of preventive respiratory management. In case of established severe BPD, respiratory support with non-invasive or invasive positive pressure ventilation is required (34, 37).

Invasive mechanic ventilation is a well-known risk factor in the development of BPD. To decrease the volu- and barotrauma related lung injury NIV strategies are introduced in neonatal respiratory management, and it has become increasingly popular over time. NIV allows infants with BPD to wean from invasive mechanical ventilation and prevents the recurrence of respiratory failure requiring re-intubation (47).

Non-invasive respiratory support has been used after extubation to reduce extubation failures, or as a primary modality for premature infants with respiratory distress syndrome, and also to prevent late respiratory morbidity/BPD for premature babies (47).

Continuous PAP (CPAP) is the first and most commonly used mode of positive airway pressure (PAP) therapy for neonatal respiratory support (48). Continuous PAP provides alveolar inflation and prevents atelectasis. The physiological benefits of CPAP such as stabilization of chest wall and upper airway, reduction of lung resistance and improvement of tidal volume, oxygenation, and functional residual capacity increase the success of extubation of preterm infants (9). The use of CPAP significantly reduced the need for invasive mechanical ventilation but the rates of CPAP failure are high. On the other hand, studies evaluating effects of CPAP on preventing BPD, showed that use of nasal CPAP did not significantly reduce the rate of BPD and death compared with the infants who were intubated early and received surfactant (49, 50).

Nasal intermittent positive pressure ventilation (NIPPV) is an alternative strategy to CPAP. It is a type of NIV delivered via nasal prongs using a mechanical ventilator. NIPPV provides mandatory ventilation at a preset rate using short inflation times, and two different airway pressure levels similar to those used with invasive ventilation. Nasal intermittent positive pressure ventilation can be applied in a synchronized mode (SNIPPV) or can be delivered independent of the infant's breathing efforts. The synchronization of NIPV is challenging (33, 51). A meta-analysis examining the benefits of early NIPPV vs. CPAP showed significantly reduced risk of extubation failure among infants treated with NIPPV. However, a meta-analysis found no difference in the risk of BPD between NIPPV and CPAP (52).

The comparison of SNIPPV vs. NIPPV, according to a meta-analysis, showed that SNIPPV was superior to NIPPV in terms of the need for re-intubation up to 1 week after

extubation. However, there was no difference in the rates of the development of BPD between these two interventions (53). Furthermore, a recent systematic review comparing ventilation strategies including NIPPV among preterm infants also showed no differences in outcomes of BPD between NIPPV and other ventilatory strategies (54).

Bilevel positive airway pressure is another form of NIV and has a similar mechanism to NIPPV. BIPAP also provides two levels of positive pressure (PIP and PEEP) at preset intervals. The pressure delivered by BIPAP is lower than NIPPV. Additionally, BIPAP provides longer inspiratory times and lower cycle rates than NIPPV and allows spontaneous breathing in contrast to NIPPV (55). Possible benefits include tiny actual breaths delivered from the small change in pressure and reflex "triggering" of spontaneous breaths via stimulation. Also, since high pressures can be used, it is better at preventing reintubation compared to CPAP (50). However, there are few studies investigating the use of BIPAP among preterm babies, and the results are inconclusive. In the first of the randomized studies in the literature, BIPAP was found to be superior to CPAP in respiratory support time, while no difference was found in another study (56, 57). In a later retrospective study, the duration of intubation was shorter in the group of <32 weeks old infants using BiPAP. The frequency of BPD was similar in all of these studies (58). Studies comparing BiPAP to NIPV also revealed no difference between the rates of the development of BPD between the two NIV modes (59).

As mentioned above, despite the common use of NIV modes, none of the NIV modes reduced the frequency of BPD. A study investigating practical differences in the use of NIV strategies across Canadian neonatal intensive care units showed that CPAP was used in all centers, but the rate of BiPAP use was 79%. According to this study, NIV practices were performed only in 61% of all cases based on local guidelines. There was also a significantly high variability in terms of settings and interfaces used. The authors of this study concluded that the long-term results of NIV would be better with optimized standardized treatments rather than various clinical practices and underlined the need for universal evidence based-guidelines on the use of NIV (60).

The data of patients with BPD are quite limited in the studies evaluating patients using long-term NIV in the literature and invasive ventilation is still a common approach for patients with BPD requiring long-term respiratory support.

CYSTIC FIBROSIS

Pulmonary involvement is the primary cause of morbidity and mortality in patients with CF. Mucus plugging, chronic inflammation, and bronchiectasis cause airflow obstruction and parenchymal damage, followed by a progressive deterioration in lung functions. Despite the improvement in CF care, chronic respiratory failure, and end-stage lung disease develop in most of the patients (61).

According to physiological studies there is an increase in respiratory load in CF patients. Respiratory muscle load, which is assessed by the esophageal pressure time products and diaphragmatic pressure time products and the elastic and the total work of breathing is increased in CF patients. This increase in respiratory load is also correlated with the progression of pulmonary function decline. However, respiratory muscle activity is preserved and central drive is normal or increased in patients with CF. Despite the preserved respiratory muscle activity and normal or increased central drive, alveolar hypoventilation occurs in CF patients with the worsening of lung disease, especially during conditions requiring an increase in minute ventilation (exercise, respiratory infections) due to the inability of the patients to increase their respiratory rates any further (62).

Central drive and chemoreceptor sensitivity are preserved during wakefulness in patients with mild-moderate CF lung disease, but alveolar hypoventilation characterized by an increase in partial arterial carbon dioxide pressure ($PaCO_2$) and decrease in partial arterial oxygen pressure (PaO_2) may occur during sleep. During sleep, there are physiological changes in central drive, respiratory muscle function and lung mechanics. Decrease in central drive and chemoreceptor sensitivity during sleep cause alveolar hypoventilation and a rise in $PaCO_2$. Respiratory muscle function is also adversely affected, especially the accessory muscles of respiration and upper airway muscles, whereas diaphragmatic contraction is relatively preserved during sleep. Altered respiratory mechanics in terms of an increase in ventilation–perfusion mismatch, an increase in airflow resistance, and a decrease in functional residual capacity, contribute to nocturnal hypoventilation (10, 62).

With the progression of pulmonary involvement and increased respiratory load, patients develop a rapid shallow breathing pattern and subsequent daytime hypercapnia (10, 62). In addition, chronic alveolar hypoxia, hypercapnia, and endothelial dysfunction due to chronic inflammation may cause pulmonary hypertension (63, 64). Pulmonary hypertension is inversely correlated with respiratory function and nocturnal oxygen saturation. Hypoxemia, hypercapnia and pulmonary hypertension indicate poor prognosis and prompts referral for lung transplantation (65).

NIV, which acts as an external respiratory muscle, reduces the number of required respiratory efforts by the patient and reduces the muscle load for a given tidal volume during an assisted breath. These effects can reverse fatigue and reduce neural drive to prevent fatigue (66). The improvement in lung and chest compliance causes a decrease in respiratory muscle load and an increase in tidal volume, in alveolar ventilation and gas exchange (10, 67).

Implementation of NIV even for a short period (during sleep, exercise) allows improvements in alveolar ventilation and gas exchange, which is a result of the increased chest wall and lung compliance and decreased cerebrospinal fluid bicarbonate concentration increase respiratory drive (62).

There are no validated criteria for timing and patient selection for the initiation of NIV, particularly in the pediatric population, despite the physiological benefits of NIV in CF patients. According to the Cystic Fibrosis Foundation recommendations, the presence of the symptoms related to hypercarbia, and a

PCO_2 level ≥55 mmHg or; $PaCO_2$ 50–54 mmHg and nocturnal desaturation, or, $PaCO_2$ 50–54 mmHg and ≥2 hospitalizations in the preceding year for hypercarbic respiratory failure are the main indications for initiation of NIV (68). The European CF Society recommends NIV according to the patient's wishes for relief of dyspnea (69).

There are several studies on the use of NIV for cystic fibrosis which reported clinical indications. According to a national survey performed in France, severe respiratory exacerbation and diurnal hypercapnia were the main indications for NIV use. NIV may also be useful for patients with an accelerated fall in lung functions and its use may be proposed to prevent or treat an acute severe respiratory exacerbations. NIV use is also an option in palliative care for end-stage CF lung disease (70, 71).

There are no studies on the effectiveness of NIV in children with CF acute exacerbations, but adult studies showed good effect of NIV during exacerbations. A study investigating outcomes of adult CF patients admitted to the ICU revealed that the patients managed with NIV had lower mortality rates compared to patients receiving invasive mechanical ventilation (72). A later retrospective multicenter study investigated the outcomes of 60 ICU admissions of 42 adult CF patients. Pulmonary exacerbation was the main reason for ICU admission (67%). NIV was used in almost 75% of admissions for pulmonary exacerbations and was efficient in two-thirds of the cases. NIV success was more frequent among patients with prior home NIV (61 vs. 36%) (73).

NIV can also be used as a first-line treatment outside the ICU to prevent the worsening of acute exacerbation. In a retrospective study, cases were treated either in the pulmonary department or in the ICU depending on the severity of the acute exacerbation. The rate of NIV use was 33% (15 out 45) and 61% (14 out 23) in the pulmonary department and ICU, respectively. There were no deaths reported in the patients treated at the pulmonary department, and the 1-year survival rate in this group was over 91%. The authors concluded that pulmonary exacerbations in CF can be safely managed in a pulmonary department via NIV, provided the medical team is experienced on the CF and use of NIV (74).

In the early studies on the use of NIV in CF, it was stated that NIV is a short term bridge for patients waiting for lung transplantation. These studies showed that NIV avoids intubation related complications such as infections and barotrauma, facilitates weaning from mechanic ventilation in the post-operative period of transplanted patients, and reduces health care costs (75). Additionally, NIV has a place in the management of patients with end-stage cystic fibrosis lung disease, who are already on a transplant waiting list or who are being evaluated for lung transplantation (75). Although the effect of NIV on survival is controversial, it is a suitable treatment option in the palliative care of patients who are not eligible for transplantation (75). Non-invasive ventilation has also been increasingly investigated outside transplant-listed patients in the later studies (76, 77).

Although there is no data in children, studies in adults showed the benefits of NIV in preservation of lung functions in advanced CF patients. Fauroux et al. evaluated long-term NIV among adult CF patients with severe lung disease, 41 patients (male/female ratio = 20/21) with advanced lung disease on NIV were compared to 41 age and gender matched controls. The ventilated group was compared to the control group at year −1, during the year of NIV initiation (year 0) and 1 year after NIV (year +1) Mean age was 23 ± 8 years in both groups. The two groups had a similar level of mean FVC 43.7 ± 11.6 and 49.1 ± 15.4 and FEV_1 at year −1. (28.2 ± 10.0 and 28.5 ± 10.1% for the ventilated group and control group, respectively). At year 0, the ventilated group had significantly greater declines in FVC (−3.6 ± 9.2 vs. +0.8 ± 8.9%, $p = 0.03$) and in FEV1 (−3.0 ± 6.7 vs. +2.6 ± 4.4, $p < 0.0001$). At year +1, the decreases in FVC (−2.1 ± 10.0 vs. −2.2 ± 9.9%) and FEV1 (−2.2 ± 6.7 vs. −2.3 ± 6.2%) were similar in both groups. Although the fall of lung function was greater in the ventilated group prior to the NIV use, NIV was associated with the stabilization of the decline in lung function in the ventilated group after 1 year of follow-up (76). In a more recent retrospective study, patients with advanced lung disease who received long-term NIV were investigated. 47 patients (30 males) were included to study. The mean age was 29 years, and the mean FEV_1 was 20.7% predicted. The analysis of clinical data of patients at 12, 24, and 36 months before and after initiation of NIV revealed that 24 of 33 subjects showed an improvement in lung function or a drop in the rate in the deterioration of lung function. The mean duration of NIV use was 16 months in this study. Although the improvement in respiratory functions was most remarkable in the 1st year, this effect was observed to continue in patients who used NIV over 3 years. (FEV_1 and FVC increased at the 1st year, 18 and 69 mL, respectively. At the 3rd year the increase in FEV1 and FVC was 43 and 142 mL, respectively). The authors emphasized that NIV may slow or reverse the decline in lung function in adults with advanced CF (77). However, the authors did not record the data of adherence to NIV in either of the studies (76, 77).

NIV can be also used for overnight ventilation in CF patients. There are many studies reporting sleep-disordered breathing (SDB) in patients with CF. A meta-analysis showed that CF patients had lower O_2 saturation levels, poorer sleep efficiency than healthy controls, but higher respiratory event indices. This study also revealed a positive correlation between nocturnal desaturation and disease severity. Sleep is negatively affected by several factors in CF patients (78). Chronic lung disease-related gas-exchange abnormalities, chronic nocturnal cough, gastroesophageal reflux, abdominal pain may cause sleep disruption and SDB in CF patients. Additionally, upper airway disease and impaired mucociliary activity may lead to obstructive sleep apnea syndrome (11). Early diagnosis and treatment of SDB may prevent cardiopulmonary complications such as pulmonary hypertension, improve pulmonary outcome, as well as psychological and cognitive health (11, 78).

According to the CF Foundation recommendations, oxygen supplementation is recommended for patients with nocturnal hypoxemia, while NIV should be considered in cases with hypercarbia (68). Nocturnal implemented NIV can prevent the fall in minute ventilation from NREM to REM sleep in patients with CF (62).

Milros et al. investigated ventilation in all sleep stages in 13 CF patients (aged 26 ± 5.9 years) with moderate to severe lung

disease and compared the results of low-flow oxygen and NIV on ventilation and gas exchange during sleep. They found that minute ventilation in REM sleep was significantly lower than in NREM sleep or wakefulness. Both low-flow oxygen and NIV increased the nocturnal oxygen saturation level. The measure of transcutaneous carbon dioxide levels revealed that the maximal change in transcutaneous carbon dioxide levels from NREM to REM with low-flow oxygen was 4.7 ± 2.9 vs. 1.6 ± 0.9 mmHg on NIV. Thus, they showed that the initiation of BIPAP decreases REM related hypoventilation (79). Patients, who were already receiving supplemental oxygen therapy, showed further improvements in nocturnal ventilation with the addition of NIV (80, 81). Another prospective, randomized, parallel-group study in adult patients with CF and sleep desaturation was recently conducted. This study compared 12 months of NIV ($\pm O_2$) to long term oxygen therapy. There were 14 patients (mean age = 28 years) in the NIV ($\pm O_2$) group and 15 patients (mean age = 31 years) in the long term oxygen group. Unlike other studies, NIV ($\pm O_2$) during sleep was associated with event-free survival, which defined as no deterioration in awake CO_2 levels, transplantation, or death, over 12 months in adults with CF (82). It should be noted that since these studies are conducted among adults, these results should be evaluated in the context of using criteria specifically established for children for example different criteria used to define hypoventilation during sleep.

A recent Cochrane review also stated that NIV, in combination with oxygen therapy improves gas exchange during sleep to a greater extent than oxygen therapy alone in people with moderate to severe CF lung disease in single night studies (83).

However, based on studies of polysomnographic data in CF patients, total sleep time, sleep efficiency, and arousals remained similar despite the use of NIV (11). But exercise capacity and scores of health-related quality of life also showed an improvement with the implementation of NIV in patients with CF (11).

NIV is also usefull as an adjunct to other airway clearance techniques, particularly in people with cystic fibrosis who have difficulty expectorating sputum (83). Studies evaluating the impact of NIV on airway clearance therapy showed that the use of NIV improved respiratory muscle performance, oxygen saturation levels and pulmonary lung functions measured by lung clearance index during a 3-month period (84, 85). Faouroux et al. investigated the effect of NIV on respiratory muscle fatigue and oxygen desaturation during chest physiotherpy in children with CF. Authors measured maximal inspiratory and expiratory pressures before and after chest physiotherapy in CF patients, who received positive pressure only during inspiration, and found a decrease in respiratory muscle performance and in oxygen saturation level. They demonstrated an improvement in muscle fatigue and desaturation with the implementation of NIV during chest physiotherapy. These results may be explained by the effect of NIV as an external inspiratory muscle, and increased lung and chest wall compliance. Non-invasive ventilation may be used with chest physiotherapy in patients with muscle fatigue and desaturation and poor tolerance of the chest physiotherapy sessions (84). Although there are no specific criteria for timing of addition of NIV to chest physiotherapy in children with CF, it may be considered in children with an acceleration of lung function decline requirement admissions. It has been shown that NIV enhances aerosol deposition in cystic fibrosis, but there are no studies investigating the integration of NIV and chest physiotherapy with nebulized treatments (25).

A study evaluating the practice on the use of NIV across pediatric CF centers in United Kingdom and Australia showed that only 0.4% percent of all patients were on NIV therapy. NIV was initiated according to a protocol only in 30% of centers. The most frequently used methods of NIV were BIPAP via nasal masks. Sleep studies were performed in less than half of the centers for the decision of initiation or follow up of NIV, and the pulse oximetry was the most used method for evaluation (86).

As discussed above, there is a physiological rationale for the use of NIV in patients with CF lung disease. However, long-term randomized controlled trials are required to determine the clinical effects of NIV and to establish validated criteria to start NIV in children with cystic fibrosis.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease represents a heterogeneous group of rare respiratory disorders and is characterized by the presence of diffuse infiltrates on lung imaging, and abnormal pulmonary function tests indicating a restrictive ventilatory defect and/or impaired gas exchange due to inflammatory and fibrotic changes of the lung parenchyma (87). A recent classification based on the patient's age, clinic findings, and radiologic and histologic characteristics have been developed. Interstitial lung diseases are grouped as ILD specific to children aged <2 years and as ILD not specific to age. While surfactant protein deficiency, neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenesis, and developmental disorders are specific to infancy, ILD related to exposure/environment insults, ILD related to systemic and immune diseases, and ILD related to primary lung parenchyma dysfunctions constitute the non-age specific group (88). Anti-inflammatory and immunosuppressive agents are the cornerstones of pharmacological therapy, while oxygen and ventilatory support are required for patients with hypoxemia and respiratory failure (9).

In ILD, increased respiratory rate, increased resistance, decreased lung compliance increase work of breathing, and respiratory load. Non-invasive ventilation is expected to correct these pathological processes, but the results are controversial in ILD patients. In adult studies, the success rate of NIV in chronic restrictive diseases was lower compared to obstructive diseases. This difference was linked to a markedly reduced inspiratory flow and tidal volumes due to decreased compliance (89, 90).

There are no studies on the NIV use among children with ILD. The study investigating 1-year outcomes of the children with a new diagnosis of ILD, submitted to the ChILD-EU Registry revealed that over 12 months, the number of the children receiving NIV was close to children receiving invasive mechanical ventilation (32 vs. 34%) (91).

Current data on the NIV use in ILD is limited to adult studies. The most common indication of NIV is the acute respiratory

failure (ARF) episode of ILD. The outcome of ARF is poor in ILD patients. Due to the potential side effects of invasive mechanical ventilation, NIV has expected to be the preferred method in stabilizing ARF, minimizing the intubation related the complications. Studies evaluating the outcomes in ILD patients during an ARF episode requiring ventilatory support found that despite palliative improvement with NIV, the prognosis was poor (17, 92) Authors stated that the NIV should be considered in less severe patients with an acute physiology and chronic health evaluation (APACHE) II score >20 because of mortality risk and high unsuccessful rate (92). A recent study evaluating risk factors for mortality in ILD patients during an ARF episode requiring ventilatory support found that the survival was better for patients receiving NIV support compared to invasive mechanical ventilation (93). The etiology of acute respiratory failure (ARF) episode is also important on the NIV response. Aliberti et al. found an improvement in oxygenation during NIV treatment in patients with ARF due to pneumonia, but not in other etiologies such as fibrosis and other triggers responsible for ARF, and they suggested to individualize NIV treatment (94).

The use of NIV in ILD in chronic hypercarbic respiratory failure was reported by Koschel et al. in a case series. They used NIV in 10 adult patients during sleep, and they showed a decrease in daytime arterial pressures of carbon dioxide and an increase in the arterial partial pressure of oxygen (95).

NIV can also be used during chest physiotherapy sessions in patients with ILD. Dreher et al. compared the 6-min walk distance (6MWD) and quality of life scores measured by short form 36 in hypercarbic ILD patients receiving nocturnal NIV patients to those who are normocarbic and not receiving NIV. They found an increase in the 6MWD and the mental score in the group who used NIV. Authors concluded that nocturnal NIV was able to improve exercise capacity and quality of life (96).

Finally, NIV may also be considered in palliative care in ILD patients. A retrospective analysis revealed that NIV was used in 29% of the ILD patients to relieve dyspnea in patients with end-stage lung diseases in 6 months prior to the death (97).

NON-CYSTIC FIBROSIS BRONCHIECTASIS

Non-Cystic fibrosis bronchiectasis is one of the most common causes of chronic lung diseases. Typical findings are persistent or recurrent (>3) episodes of chronic wet or productive cough, coarse crackles and digital clubbing, and the presence of bronchial dilation in high-resolution chest tomography (HRCT) (98). There is an obstructive pattern in pulmonary function tests, a concomitant restrictive pattern may also occur. As the disease progresses, there is an increase in the ventilation/perfusion mismatch, and hypoxemia followed by the development of hypoventilation and hypercapnia. Infections, immune deficiencies, primary ciliary dyskinesia (PCD), and recurrent aspirations are the main causes of non-CF bronchiectasis. Between 19 and 55% of the patients with non-CF bronchiectasis may be considered idiopathic as underlying etiology may not be identified (98, 99). The objectives of the management in non-CF bronchiectasis are the treatment of respiratory infections and augmentation of airway clearance with chest physiotherapy to prevent the decline in lung functions and to improve quality of life (98, 99).

The data on the use of NIV in children with non-CF bronchiectasis is scarce. According to a retrospective adult study investigating trends in NIV use and outcomes in COPD and non-COPD patients with acute respiratory failure over 15 years showed that the number of patients with severe bronchiectasis requiring NIV is decreased. This study also revealed that the efficacy rate was lower in the non-COPD group (bronchiectasis, ILD) compared to COPD patients (100).

NIV is increasingly used in non-CF bronchiectasis patients with acute respiratory failure. The adult studies investigating the efficacy of NIV in non-CF bronchiectasis patients with acute respiratory failure due to exacerbations or other etiologies such as pneumonia showed comparable results between NIV and invasive mechanical ventilation. A retrospective study investigating the results of NIV and invasive mechanical ventilation use among 99 patients with ARF and non-CF bronchiectasis revealed that NIV was used in 67% of the patients, and the success rate was 65%. The efficacy in correcting blood gases was similar in both groups. Also, the total duration of stay in the hospital was similar in both groups. The authors concluded that the NIV use is a feasible treatment option for the management of ARF with non-CF bronchiectasis (101).

Long term use of NIV was investigated in adults with non-CF bronchiectasis and chronic respiratory failure. Benhamou et al. studied long-term efficacy and tolerance of NIV in 14 patients with non-CF bronchiectasis and chronic respiratory failure and compared with those who received long-term oxygen support only. NIV use was associated with the reduction of the days of the hospitalization, but partial oxygen saturation and the overall survival rates were similar in both groups. Non-invasive ventilation was well-tolerated in 11 of 14 patients (102).

In another retrospective study on the long-term effects of NIV in adults with non-CF bronchiectasis and chronic respiratory failure, blood gas levels, duration of hospitalization, and questionnaires to determine the patients' perception of the benefits of the treatment were evaluated before and after the initiation of NIV. The median duration of NIV use was 26 months. With the initiation of NIV, a stabilization in PCO_2 levels was recorded. Duration of hospitalization between 12 and 24 months after starting NIV was decreased compared to 1 year before the initiation of NIV. An improvement in the quality of life was also observed (103).

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans is a rare chronic lung disease characterized by obstruction of the small airways. Bronchiolitis obliterans is mainly caused by infections, inhalation of toxic fumes, connective tissue diseases, and after hematopoietic stem cell transplantation. The main histological findings of BO are fibrosis and inflammation of terminal and respiratory bronchioles (104, 105). Tachypnea, hypoxemia, and persistent wheezing are common symptoms. It has been also reported

that children with BO also have sleep-disordered breathing, and increased risk of nocturnal hypoxemia which is correlated with the severity of lung functions (106). Prognosis and treatment differ in BO patients based on the etiology. While patients with post-infectious BO have chronic and slowly progressive course, other etiologies may cause a rapidly progressive disease.

There is still no evidence regarding treatment and the mechanisms of the development of BO in children. The current management of BO is based on the studies among adult BO patients mainly caused by lung transplant and hematopoietic stem cell transplantation. The management includes systemic and nebulized anti-inflammatory agents, nebulized bronchodilators in addition to general supportive care including respiratory support, pulmonary physiotherapy, and nutritional support, and children with BO should be followed up by a multidisciplinary team in specialized centers (105).

There is no study on the application of NIV in post-infectious BO patients. In a case report, the importance of the analysis of the work of breathing and respiratory mechanics to optimize of NIV treatment for BO was addressed. NIV following physiologically determined settings, reduced hyperinflation, decreased respiratory rate, and normalized the inspiratory time/total duty cycle ratio in an infant with postinfectious BO, which resulted in a decrease of work of breathing (107).

COMPLICATIONS AND ADHERENCE

There are no specific references for compliance and adherence of NIV in children with chronic lung disease. Interface-related complications are common in the use of long term NIV. Skin trauma caused by prolonged use of masks is the most common complication. Skin lesions were reported in half of the patients after 6-month use of NIV via nasal masks (108). Eye-irritation caused by air leaks may also occur due to inappropriate sizes of masks. In small children, nasal or facial masks can cause mid-face hypoplasia and malocclusion (109). Additionally, it can lead to neurodevelopmental delay by acting as a physical barrier to social interaction. The development of newer interfaces such nasal pillows may cause fewer complications with minimum pressure points (4). Mask fitting and strap tension should be optimized to avoid skin trauma. Alternating interfaces and use of protective skin gel pads are also useful (62, 109). Nasal pillows, nasal masks, nasobuccal masks, total face masks, and mouthpieces are interfaces used in NIV for children. From those, nasal pillows, which provide minimal skin contact and enhanced comfort, can be used for children aged 5–7 years or older (4).

Other complications are associated with the delivery of positive pressure. Gastric distention, gastroesophageal reflux, and feeding intolerance can be seen with high pressures. Another associated risk is pulmonary aspiration caused by vomiting while wearing an oronasal or face mask. High pressures may also lead to nasal congestion. These complications can be managed by decreasing the airway pressures and using nasal masks (4, 62).

Adherence to NIV is one of the major barriers to treatment in children. Currently there is no specific definition for adherence in children. Adherence definitions used in child studies in the literature are generally adapted from adults, although the sleep structure and duration of children are different from adults. There are several factors affecting adherence, including patient characteristics, devices and masks used, pressure settings, side effects, and psychological and social factors (110). Educational and behavioral interventions may improve adherence, peer support groups and individualized strategies are also recommended (109, 110).

Ramirez et al. investigated adherence to NIV in 62 patients (mean age, 10 ± 5 years) with three underlying disease categories including five children with chronic lung disease. Mean objective adherence was extremely high in that study with a mean use of 8.17 ± 2.30 h per night and 72% of the patients using their CPAP or NIV >8 h per night. Treatment adherence was not correlated to the type of underlying disease or the efficacy of NIV assessed on the nocturnal gas exchange. Authors commented that the excellent level of compliance in their population may be explained by the fact that NIV was initiated and followed in a dedicated pediatric NIV unit (111).

Another study evaluating NIV adherence, adherence barriers in patients with DMD using nocturnal NIV found that mask discomfort was the most commonly reported adherence barrier. The assessment of the psychosocial functioning of patients and their caregivers revealed that caregivers' barriers and child internalizing symptoms predicted lower NIV adherence, and authors recommended multidisciplinary approach to improve adherence in children (112).

CONCLUSION

NIV is an effective treatment for chronic respiratory failure and sleep-disordered breathing including hypoventilation in children with chronic lung diseases. NIV reduces the need for invasive ventilation in some incidences and allows children to live with their families at home. The use of NIV in children with chronic lung disease is increasing worldwide, as a result of improvements in the survival rates of these children. NIV can be effective for acute asthma exacerbations in children. Children with BPD also could benefit from NIV support however no differences on long term benefits have been found between CPAP and NIV. There are adult studies supporting the use of NIV in patients with bronchiectasis and ILD. However, there are no studies investigating the effect of long-term NIV use among children with chronic respiratory diseases, except CF, which shows that the application of NIV results in the stabilization of the decrease in lung functions in advanced lung disease (76). Also, NIV may be a useful adjunct to physiotherapy in CF children. The heterogeneity of the diseases and ages of the patients requires close monitoring by an experienced team. Complications are mainly related to interfaces and positive pressure and these side effects can often be managed by applying the appropriate interfaces and settings. This approach is also important to improve the adherence. Limited number of contraindications such as severe cystic/cavitatic lung

disease should also be kept in mind during evaluating the suitability of the patients for NIV. Future studies are required to determine the main criteria for NIV use and long- term benefits for these patients including the effect on the quality of life.

AUTHOR CONTRIBUTIONS

EA wrote the manuscript with support from RE. UK and RE reviewed and supervised the manuscript. All authors contributed to the manuscript and approved the submitted version.

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REVIEW
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Follow-Up and Monitoring of Children Needing Long Term Home Ventilation

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Once continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) is started in a child, and the child is discharged home, follow-up needs to be organized with regular visits in order to check the tolerance and efficacy of the treatment. But there is a lack of validated clinical guidelines, mainly because of the heterogeneity of the ventilator servicing, the costs and health care systems among countries. Therefore, visits timing and strategies to monitor CPAP/NIV are not clearly defined. Moreover, depending on various factors such as the underlying disorder, the medical stability, the age of the child, and socio-economic factors, follow-up usually ranges between 1 month and 3–6 months, or even 1 year following treatment initiation, with an overnight hospital stay, an out-patient visit, a home visit, via telemonitoring or telemedicine, alone or in combination. Apart from clinical evaluation, nocturnal oximetry and capnography monitoring and/or poly(somno)graphy (P(S)G) are usually carried out during the follow-up visits to monitor the delivered pressure, leaks, residual respiratory events and synchrony between the patient and the ventilator. Built-in software data of CPAP/NIV devices can be used to assess the adherence of treatment, to monitor pressure efficiency, leaks, asynchronies, and to estimate the presence of residual respiratory events under CPAP/NIV if P(S)G is not available or in alternance with P(S)G. The possibility of CPAP/NIV weaning should be assessed on a regular basis, but no criteria for the timing and procedures have been validated. Weaning timing depends on the clinical condition that justified CPAP/NIV initiation, spontaneous improvement with growth, and the possibility and efficacy of various upper airway, maxillofacial and/or neurosurgical procedures. Weaning may be allowed in case of the disappearance of nocturnal and daytime symptoms of sleep-disordered breathing (SDB) after several nights without CPAP/NIV and the objective correction of SDB on a P(S)G. But no parameters are defined. In any case, a long term follow-up is necessary to ascertain the weaning success. Large prospective studies, together with international and national guidelines, are required in order to build evidence for standardizing practice for the follow-up and weaning of CPAP/NIV in children.

Keywords: noninvasive respiratory support, child, follow-up, monitoring, hospital, home, weaning

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INTRODUCTION

Children receiving home noninvasive mechanical ventilation, by continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV), should be followed with regular visits in order to check the tolerance and efficacy of the treatment. The follow-up strategy depends on various factors, such as the underlying disorder, the medical stability, the age of the child, and socio-economic factors, with no clear recommendations concerning follow-up visits and evaluation of efficiency of ventilation for children (1). The follow-up may consist of an overnight hospital stay, an outpatient visit, a home visit, a visit via telemedicine, alone or in combination. The evaluation of the respiratory support efficacy relies on sleep studies (poly(somno)graphy, P(S)G), nocturnal pulse oximetry (SpO_2) and capnography (CO_2) monitoring and/or respiratory support devices data with direct access of the data or via telemonitoring.

Follow-up may also help to identify patient's improvements that may prompt a weaning attempt from home CPAP/NIV. Indeed, as CPAP/NIV is usually initiated in children presenting with various medical conditions with different clinical evolutions and/or potential strategies (surgery, etc.), the need to reassess the utility for this ongoing treatment is crucial, as many children may be weaned from their respiratory support. Here again, no recommendations are available to guide the weaning process that is therefore based on clinical practice (2).

This review describes the available strategies based on the experience of worldwide centers or consensus papers, as evidenced-based guidelines for the follow-up and weaning of children receiving CPAP/NIV are lacking.

FOLLOW-UP

Visits

Prior to hospital discharge, the patients and/or families must have received adequate education and training for the use of the home noninvasive respiratory support (3). Following hospital discharge, the Canadian Thoracic Society recommends that "the first visit and the frequency of subsequent visits should be tailored to the child and family's need" (1), based on a consensus for pediatric home ventilation (4). They suggested, based on a review of the literature, that the first visit should occur within the first month and no later than 3 months after home discharge (1). Following the first visit, the number and timing of the subsequent follow-up visits will depend upon the condition of the child and the evolution of the disease. Reassessment is recommended at least every 6–12 months (5, 6), even though more frequent follow-up visits may be necessary in many young children with additional unscheduled visits.

In-Hospital and Outpatient Clinic Visits

No studies have evaluated the optimal frequency and type of follow-up visits and monitoring resources for children using CPAP or NIV. Clinic follow-up visits may occur monthly to annually, depending on the patient's condition and underlying disease (3, 7).

In-hospital visits may be reserved for follow-up sleep studies, together with the assessment of the patient's ventilator use and the review of training and education of the patient and family when necessary (3, 8–10). According to our experience in children treated by CPAP, in-hospital P(S)G on CPAP may be limited to children with persistent symptoms of obstructive sleep apnea despite good objective adherence to treatment or when the nocturnal gas exchange and data obtained from built-in monitoring devices are abnormal or non-interpretable (11). Concerning patients treated by NIV, in-hospital P(S)G should be more systematic (10, 12), even though nocturnal gas exchange and data obtained from built-in monitoring devices (with breath-by-breath analysis of built-in software) may be sufficient for follow-up in a majority of patients (13).

Outpatient clinic visits allow to check for the patient's clinical condition, the adherence to treatment and the review of the ventilator data and needs for parents and child's retraining and education (8, 9, 11, 14, 15). They are feasible in patients treated by CPAP (11), but also by NIV (7). However, outpatient clinic visits rely on the availability of homecare providers or dedicated healthcare staff to assess the patient at home. Indeed, due to the limited time available during an outpatient clinic visit, assessments such as transcutaneous gas exchange may not be feasible and may not be representative of a nighttime monitoring. Therefore, a close collaboration with homecare providers is essential as they can do frequent home visits and send out the ventilator data and/or overnight recordings of gas exchange to the hospital team, prior to the outpatient clinic visit, which enables rapid adjustments of the settings when necessary, during the first weeks of treatment which are crucial for adherence, but also during follow-up (**Figure 1**).

Home Visits

Healthcare systems vary according to countries. Some centers have teams of professionals (mainly nurses, respiratory therapists but also physicians) who can perform home visits between hospital visits, while other centers collaborate with home healthcare providers who can visit the child and family (1, 9, 11, 14, 15). Several types of home service providers may exist with different medical functions (7). In a national survey in Canada, Rose et al. (7) reviewed the procedures or tests that were carried out during follow-up visits. They comprised regular ventilator checks, ventilator compliance/adherence assessment, overnight or daytime oximetry, overnight transcutaneous CO_2 monitoring, spirometry and P(S)G, with an exclusive management at home in 53% of the cases. However, it is not clear in this review if tests such as spirometry or PSG were also carried out at home.

No published study compared hospital visits to home visits concerning follow-up strategies, probably because most patients may not be followed exclusively at home for their respiratory support treatment.

Telemedicine

Several studies reported the use and effectiveness of telemedicine for the follow-up care of children on home mechanical ventilation, with an increased interest in this strategy (7, 16–21). Telemedicine was first used to follow the children on home

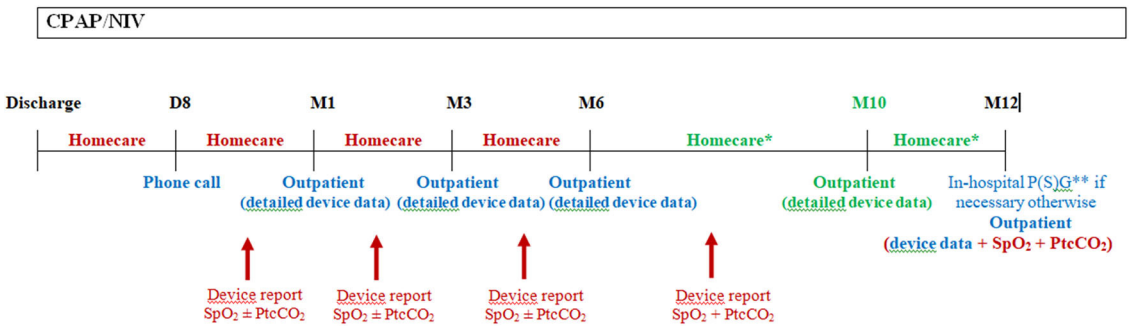

FIGURE 1 | Schema of the first year follow-up in our center following hospital discharge. Following hospital discharge, a phone call to the family is done after 1 week by our staff (usually by a nurse specialized in therapeutic education) to ascertain the correct comprehension of the treatment and deal with the potential problems with the device and interface. A home visit is also performed by the homecare provider. A CPAP/NIV device data report and nocturnal gas exchange are done by the homecare provider and send to the hospital staff prior to the outpatient visit at 1 month following discharge. The same is usually repeated at 3, 6, and 10 (for NIV patients) months following discharge. In patients with CPAP, nocturnal gas exchange monitoring is not necessary at each homecare provider visit if the patient had no residual respiratory events under CPAP with a correction of gas exchange at 1 month follow-up. Moreover, transcutaneous carbon dioxide monitoring is not mandatory in patients under CPAP if they were not hypercapnic at the 1 month control. In this case, only nocturnal SpO_2 may be performed at home if necessary for the following visits. Supplementary homecare provider or outpatients visits may be necessary in severe patients or in families with difficulties. And in-hospital admission may be necessary in case of clinical deterioration or if CPAP/NIV adjustments needs to be done with P(S)G. This schema is applicable for children who do not require surgery within the first year or who are not weanable, otherwise CPAP/NIV should be stopped and P(S)G and/or nocturnal gas exchange should be scheduled after the requested time following surgery or CPAP/NIV discontinuation due to spontaneous improvement. D, day; M, month; Homecare, homecare provider visit; Outpatient, outpatient hospital visit; SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide; P(S)G, poly(somno)graphy. In red: homecare services; In blue: hospital services; In green: only for patients with NIV. * At least 1 visit between M6 and M12, for patients with CPAP. ** Ideally P(S)G for patients with NIV.

mechanical ventilation in the 1990s, and telemedicine is now largely implemented in many centers, to facilitate the patient's care and/or to limit the number of clinic visits or in-hospital admissions (19, 21). Studies showed a good acceptance by the patients and families, and by the paramedical and medical teams (20, 21). The telemedicine procedure associated real-time discussions with the patient, the family and professionals, the transmission of clinical data, SpO_2 and transcutaneous CO_2 monitoring, spirometry and ventilator data (16, 17, 21). However, as stated by Chuo et al. (16), "There is a "booming use" of telehealth without a corresponding "booming understanding" of its impact, advantages, and limitations." Moreover, telemedicine may also cause an increased number of hospitalizations, oupatients visits, telemedicine consultations or home care visits (16), therefore "a more comprehensive cost benefit analysis is needed" together with legal clarity as legal problems associated with telemonitoring remain controversial. Indeed, although well accepted by patients, families and medical teams, the use of telemedicine needs further investigations as it is not clear if it actually decreases cost or improves outcome (1). The ERS statement on telemonitoring of ventilator-dependent patients concluded that "despite the hopes in telemonitoring as a means to face these problems, much more research is needed before considering telemonitoring a real improvement in the management of these patients" (17).

Monitoring

Effectiveness of CPAP/NIV should be assessed on a regular basis. Monitoring should include ideally a P(S)G or nocturnal SpO_2 and capnography recording, if P(S)G is not available. The monitoring should be performed every year at a minimum. Moreover, the respiratory support device built-in software data should be gathered at each clinic or home visit to assess the efficiency of ventilation, the adherence to the treatment, as well as the history of alarms and other events. Ideally, the same data used during in-hospital or outpatient visits to monitor the efficiency of ventilation and the clinical condition of the patient should be available during the home visit. **Figure 1** shows our clinical practice for the first year follow-up of patients with CPAP/NIV, with the different monitoring resources available in our center.

Poly(somno)graphy (P(S)G)

International guidelines recommend to periodically perform PSG to revaluate children on CPAP (22). In children under NIV, with diseases such as neuromuscular disorders and alveolar hypoventilation syndromes, they proposed that a periodic reassessment with PSG and CO_2 monitoring should be scheduled according to the child's growth rate and degree of clinical stability, but it should be at least annual (22, 23). Recent guidelines also recommended performing PSG to assess the effectiveness of ventilation every 6 month or every year (1). However, little evidence is available in the literature. Indeed, only two studies documented the usefulness of follow-up respiratory support titration sleep studies in children. Tan et al. (24) reported changes in the respiratory support settings in 66% of children and concluded that titration PSGs "lead to important management changes in children on respiratory support." In the second study 53% of the PSG studies led to a modification in ventilator settings (25). The authors concluded that their study suggests that consequent changes in respiratory support settings allow an improvement in symptoms and that their findings support the current guidelines. PSG may also be valuable as it also allows

recording of the mask pressure in order to monitor the delivered pressure, but also detects leaks and patient-ventilator synchrony (3), as well as identifying and characterizing residual respiratory events (26, 27). Whether P(S)G should be done only during in-hospital overnight or also at home (23) is not clear, because of the lack of studies reporting the use and feasibility of P(S)G at home in children receiving noninvasive respiratory support (28, 29).

However, the review of the experience of large centers highlights the fact that not all the centers are doing PSG, and that even when possible, the sleep studies are not done on a regular basis in all patients (1). This can be explained in part by the limited accessibility to sleep centers or to the confidence in home SpO_2 and CO_2 monitoring and respiratory support device data.

Nocturnal Pulse Oximetry and Capnography Monitoring

Guidelines usually recommend that, at minimum, overnight SpO_2 and CO_2 recordings should be available for the assessment of effectiveness of ventilation (23). However, as for respiratory support initiation, criteria to ascertain efficient ventilation are not clearly defined (30). Overnight CO_2 monitoring is essential as normal SpO_2 is not necessarily indicative of effective ventilation (3, 31, 32). The timing of follow-up nocturnal gas exchange is not defined, however the monitoring should at least be repeated if the ventilator settings are changed, or following an acute respiratory exacerbation. Overnight SpO_2 with $PtcCO_2$ recording should be performed more frequently in patients with NIV as numerous asymptomatic patients remain hypercapnic during sleep despite NIV use, or due to disease progression and needs for settings adjustments (**Figure 1**).

Regular assessment at home of the efficiency of ventilatory support and gas exchange recording appears to be consensual (1, 23). Indeed, studies reported feasibility and positive impact of home assessments because the child and family are in their usual environment (9, 23, 33). Either homecare providers or institutional care staffs are in charge of such monitoring, but the parents are also able to collaborate quite well (33).

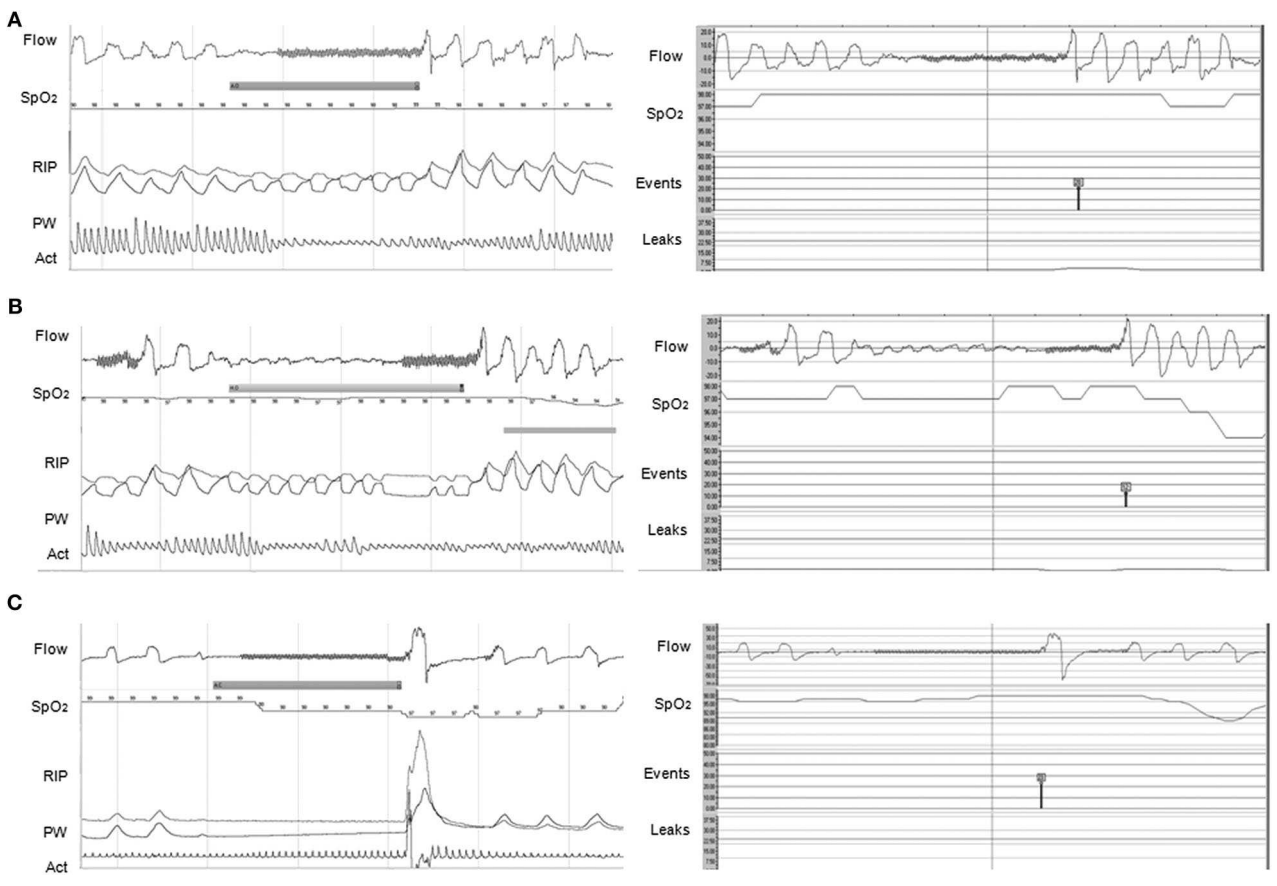

FIGURE 2 | Agreements between PG (left panel) and CPAP (right panel) software for the events detection. **(A)** Obstructive apnea without 3% OD correctly scored by CPAP software (red symbol); **(B)** Hypopnea with 3% OD on PG. The event was scored as obstructive apnea on the CPAP because of the end of the event (red symbol); **(C)** Central apnea of >20 s but no 3% OD, possibly due to an artifact on SpO_2 (note the artifacted pulse wave plethysmography), on PG compared to a central apnea of >20 s with 3% OD on CPAP (black symbol). On PG, Flow is expressed in L/min; SpO_2 in %; RIP, respiratory inductance plethysmography; PW, pulse wave plethysmography; Act, actimetry. On CPAP software (ResScan™, ResMed): Flow is expressed in L/min; SpO_2 in %; Events represent the type of automatic scored event; Leaks are expressed in L/min. The continuous line represents the threshold of excessive leaks (24 L/min). CPAP devices were AirSense 10 **(A,B)** and S9 Elite **(C)**. (1 min period-window) From Khirani et al. (37).

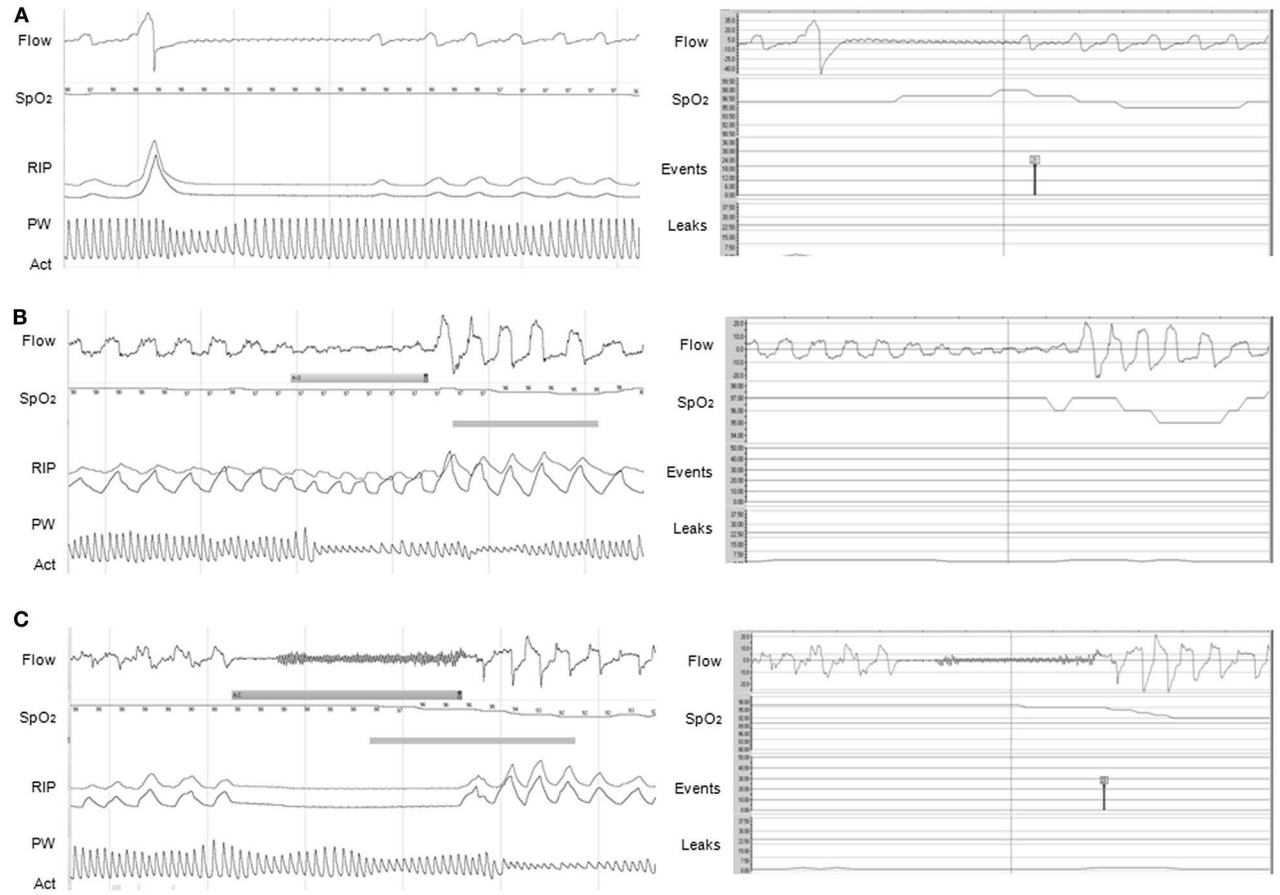

FIGURE 3 | Discrepancies between PG (left panel) and CPAP (right panel) for the events detection. **(A)** Apnea preceded by a sigh, not scored on PG but automatically scored on CPAP (black symbol). Note the presence of a 3% OD on CPAP, not present on PG; **(B)** Obstructive hypopnea with consecutive 3% OD scored on PG but not scored automatically on CPAP; **(C)** Apnea with 3% OD scored as central on PG because of the absence of inspiratory effort, but falsely characterized as obstructive on CPAP (red symbol) (3% OD also present on CPAP). On PG, Flow is expressed in L/min; SpO_2 in %; RIP, respiratory inductance plethysmography; PW, pulse wave plethysmography; Act, actimetry. On CPAP software (ResScan™, ResMed): Flow is expressed in L/min; SpO_2 in %; Events represent the type of automatic scored event; Leaks are expressed in L/min. The continuous line represents the threshold of excessive leaks (24 L/min). CPAP devices were S9 VPAP ST **(A)** and AirSense 10 **(B,C)**. (1 min period-window) From Khirani et al. (37).

Analysis of Data Obtained From Built in Monitoring Devices

Data from noninvasive respiratory support devices are widely used in clinical practice as important improvements have been made on the built-in software of CPAP/NIV devices (34, 35). Data such as adherence and effectiveness of ventilatory therapy are available, even though the type and number of available data vary according to the device (36). However, caution must be taken about interpretation of those data and technical specificities of the devices, as they are designed for adult patients and not for the pediatric population. Indeed, all the devices have manufacturer recommendations concerning the minimal weight of the patient. The device may therefore not be able to detect the breathing pattern of a child with a body weight below the minimal recommended weight, and thus may underestimate the real ventilator use by the patient and display erroneous data.

Concerning CPAP or autoCPAP, data such as adherence, unintentional/intentional leaks, ventilation (tidal volume, minute ventilation, respiratory rate), pressure level, and residual respiratory events may be available. Breath-by-breath airflow and pressure curves can be downloaded from the majority of CPAP devices, allowing a more accurate overview of nighttime use and breathing pattern, ideally with the display of SpO_2 directly in the software, and potential adjustments of the settings (**Figure 2**) (37). However, caution should be applied when reviewing the residual respiratory events and the apnea-hypopnea index data, as the algorithms for residual respiratory events on CPAP/NIV devices are based on adult criteria and do not follow the AASM scoring (**Figure 3**) (37, 38).

Concerning NIV, here again adherence, leaks, ventilation and residual respiratory events may be reviewed. Additional data such as patient-ventilator asynchronies may also be identified on the breath-by-breath data review (34). In many instances, residual respiratory events and patient-ventilator asynchronies can be managed by adjusting the ventilator settings and reviewing the ventilator data

TABLE 1 | Proposed criteria for a weaning attempt from continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV).

Major criteria	• disappearance of nocturnal and daytime symptoms of sleep-disordered breathing after several nights without CPAP/NIV • (snoring, sweating, arousals, labored breathing, change in behavior or attention) • percentage of recording time spent with a $SpO_2 \leq 90\% < 2\%$ • percentage of recording time spent with a $PtcCO_2 \geq 50$ mmHg $< 2\%$ • obstructive apnea-hypopnea index < 10 events/h on a poly(somno)graphy
Minor criteria	• minimal $SpO_2 > 90\%$ • maximal $PtcCO_2 < 50$ mmHg • oxygen desaturation index ≤ 1.4 events/h

Adapted from Mastouri et al. (1).
SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide.

without the need of P(S)G, but in some cases P(S)G may be necessary (35).

Once again, no timing has been defined for the assessment of device data. However, the access to the respiratory support device data is becoming easier, as daily wireless transfer of data is now possible from many devices (36). This not only allows the patient to review their own therapy data, but also the homecare provider and healthcare staff to access remote monitoring of cloud-based data. The data can also be manually downloaded directly from the device during the in-hospital or outpatient visits. More detailed data such as breath-by-breath airflow and pressure curves from the ventilator are not still available through telemedicine. Availability of those data would allow early detection of changes, prompting rapid intervention and, potentially, prevention of hospital admission or prediction of respiratory exacerbations, even though data trends may be enough (35, 39). Indeed, telemonitoring of adherence is reliable—provided that the child's airflow is correctly detected by the device—and clinically useful as a good adherence to CPAP/NIV contributes to the improvement of clinical outcome. Irregular use of CPAP/NIV or increased use may indicate the necessity to review the patient for familial barriers to adherence or clinical course (poor tolerance, poor acceptance by the child and/or family, clinical deterioration, clinical improvement that may prompt weaning). Telemonitoring of leaks may be very helpful, as leaks may cause discomfort, poor adherence, patient-ventilator asynchrony and suboptimal efficiency of the ventilation to correct respiratory events, which should prompt intervention at home for adjustments and education. Telemonitoring of other data such as respiratory rate to predict respiratory exacerbation or clinical deterioration needs further research (39).

Follow-up review of the device data should be accompanied by at least SpO_2 monitoring (at best SpO_2 and transcutaneous CO_2, that can now both be connected directly to some respiratory support devices). The efficacy of adjustments following leaks correction, correction of residual respiratory events or asynchronies should be ascertained by the normalization of nocturnal gas exchange (35). Future studies should focus on the interest of the combination of nocturnal gas exchange and built-in software data vs. PSG for the follow-up of CPAP/NIV.

WEANING

The possibility of CPAP/NIV weaning should be assessed on a regular basis, but no criteria for the timing and procedures have been defined. Indeed, according to the disease, clinical evolution, and surgery strategy, many children, mostly with obstructive sleep apneas, may be weaned from their respiratory support (2, 8–10, 40, 41). P(S)G should be performed to confirm CPAP/NIV weaning, however when P(S)G is not feasible or available, the lack of sleep-disordered breathing symptoms and normal nocturnal gas exchange during sleep without CPAP/NIV may be a valuable alternative (9, 41). As there are neither recommendations nor guidelines for weaning children from ventilator support, in our clinical practice which concerns mainly patients with complex, genetic and rare diseases, a weaning trial is considered when four major criteria are fulfilled with at least two minor criteria (**Table 1**) (41). In clinical practice, however, the situation is not always so clear-cut and individual particularities should be considered such as the age of the patient, his/her pathology, the tolerance/acceptance and the subjective benefit of CPAP/NIV, and its potential side effects such as skin injury or facial deformity.

Due to the long lasting effects of CPAP/NIV, a delay of at least 2 weeks is recommended without respiratory support prior to a sleep study during spontaneous breathing (41). Indeed, several mechanisms may account for this prolonged benefit, such as an attenuation of mucosal edema, a reduction of sleep fragmentation which is known to worsen airway collapsibility, an improvement of the hypercapnic ventilatory response, and an increase in upper airway muscle tone. In patients with abnormalities of the upper airways, corrective surgery may cure obstructive sleep apneas. A minimal delay corresponding to the timing associated with the maximal benefit, lasting ∼2–6 months according to the type of surgery, is recommended prior to performing a sleep study during spontaneous breathing. Finally, a progressive reduction of CPAP or NIV tolerance or compliance, in the absence of any problems, may be due to a spontaneous improvement of sleep disordered breathing, as it can be observed in infants with Pierre Robin syndrome or laryngomalacia (41). A long term follow-up is mandatory following CPAP/NIV withdrawal in children with associated disorders, as a relapse of obstructive sleep apnea may occur, particularly in syndromic children (41).

Concerning the children who discontinued CPAP/NIV due to poor tolerance or acceptance, alternative strategies may be proposed in selected patients (see the associated review in this series on "Which options when NIV fails"). Strategies such as intensive psychological and play specialist support (10) or medical hypnosis (42) can also be tested in patients who do not tolerate any interface or having other difficulties.

CONCLUSIONS

Whether the evaluation of the effectiveness of home CPAP/NIV is performed at home or in-hospital, the assessments need to be done on a regular basis, ideally using the same monitoring resources. Due to the absence of evidence-based guidelines, follow-up strategies vary according to clinical

practice but should aim to move toward building evidence for standardizing practice. Multicenter studies, together with international and national guidelines, are required to build evidence for standardizing practice for the follow-up and weaning of CPAP/NIV in children.

AUTHOR CONTRIBUTIONS

SK is the main author of the manuscript. BF, AA, LG, AL, and TT contributed to the management of the children followed in our center and the writing of the manuscript. All the authors approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Noninvasive Ventilation in Palliative Care and Ethical Dilemma

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Significant difference exists between validated indications for noninvasive ventilation (NIV) use in children and current real life practice. Lately, dedicated centers have reported exponential growth of NIV use in children and adolescents. Upper airway obstruction, neuromuscular diseases, chronic lung/thoracic conditions, and central respiratory drive failure remain the most prevalent indications. However, the need to alleviate respiratory failure related distress has been increasingly recognized in several other conditions. Palliative care in children with life limiting disorders is a complex continuum of activities. In order to provide the most appropriate care for the patients and their families, the management often oscillates between actively curative and purely supportive actions. Despite unprecedented therapeutic advancements, several neurologic, metabolic, hemato-oncologic, respiratory, and other rare diseases remain with no curative options. Besides, attentiveness to relive suffering, awareness, and availability have moved the boundaries of NIV use toward conditions formerly not considered suitable for such care. Still, NIV has limitations and can, if sustained in inappropriate circumstances, fail to provide relief. A structured professional frameshift should be available for support and ethical guidance in order to provide confidence to patients, families and all the involved caregivers.

Keywords: noninvasive ventilation, pediatric, palliative care, ethics, decision-making

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INTRODUCTION

Over the last decades, noninvasive ventilation (NIV) has become an established treatment modality in children. Technical advancements and availability of suitable interfaces have expanded its use in patients with diverse medical conditions. Long term NIV has been shown to positively influence many important disease outcomes. However, a large gap still exists between proven benefits and real-life use of this rapidly evolving respiratory support (1).

Many severe pediatric conditions have been linked to long term NIV, notably the neuromuscular diseases (NMD). A lot of such illnesses still lack causative treatments. Thus, appropriate respiratory care represents an important part of patients' management throughout the entire disease course.

The need for dedicated palliative care has been recognized in these children. Pediatric palliative management often spans over long time periods. Several specific aspects have been identified in these circumstances, particularly the fluctuating balance between adequate measures of active treatment and palliative support (2).

NONINVASIVE VENTILATION

The main goal of NIV is to appropriately sustain the ability of the respiratory system to meet the body's metabolic demands. Studies confirm that NIV can adequately relieve dynamic obstruction in the large airways, support the respiratory pump function in NMD and chest abnormalities, alleviate breathing in patients with parenchymal lung disorders and back-up diseased central breathing control (3).

An important advantage of NIV is its time-limited activity and respect for the patient's body integrity. Patients may need support only during certain activities or on demand like when sleeping, speaking or eating. Such respiratory aid is possible through a removable interface and does not interfere with person's life when breathing assistance is not essentially needed.

NIV has a clear survival benefit in many severe progressive illnesses, especially in NMD like spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) (4, 5).

PEDIATRIC PALLIATIVE CARE

Pediatric palliative care aims to appropriately relive symptoms, sustain quality of life and support the whole family of the affected child. Provided activities should be oriented toward reliving physical, psychological, social, and spiritual suffering in patients and their family members (6).

The Guide to Children's Palliative Care (2) comprehensively defines four categories of patients with life-limiting and life-threatening conditions also known as the "Together for Short Lives" (TfSL) pediatric palliative care categories. Category 1 includes diseases where curative treatment may be feasible but can also fail. These are predominantly children with hemato-oncological conditions and congenital heart disease. Category 2 contains conditions where premature death is inevitable, but available treatment can importantly prolong life and its' quality. Several NMD and congenital metabolic conditions have lately moved to this group due to therapeutic advancements. Category 3 lists progressive conditions without curative treatment options. Provided activities cannot stop disease progression and mainly aim to improve the quality of life. A lot of neurologic and metabolic conditions still remain in this category. Category 4 consists of irreversible but non-progressive conditions causing severe disability leading to susceptibility to health complications and likelihood of premature death. These are patients that suffer from injury related central nervous system damage.

In contrast to the general beliefs that palliative care predominantly concerns end-stage cancer patients, conditions in categories 2–4 affect the large majority of children in need of palliative management nowadays. Only a dedicated multidisciplinary palliative team can offer optimal support to the affected children and their families (7).

Relief of dyspnea and strenuous breathing represent the key elements of palliative care. Hunger for air is one of the most frightening symptoms for children and their parents. It is often reported to cause considerable suffering of the affected patients and even prolong parental grief (8).

Management of dyspnea in children with advanced respiratory conditions remains challenging. Several possibilities should be considered. It is important to maintain good airway hygiene. Sensation of an air draft to the face (like the use of hand held fen) and other nonpharmacological activities can reduce anxiety in patients and caregivers. A number of pharmacological options are also available; especially opioids, anxiolytics, and diuretics. Besides, providing supplemental oxygen and NIV can be beneficial (9).

NONINVASIVE VENTILATION IN PEDIATRIC PALLIATIVE CARE

Only a modest number of publications report on the use of NIV for palliative purposes in children even though this respiratory support modality is increasingly used in numerous pediatric life-limiting diseases.

Clinicians consider NIV as an important tool in palliative care aimed at providing comfort to patients, relieve suffering, and improve quality of life of both children and their families. A contemporary survey on the use of NIV in pediatric palliative care (10) gathered responses from 73 participants working at University hospitals. Sixty-two percent were intensivists, a quarter pediatric pulmologists and 11% palliative medicine consultants. Large majority (84%) considered the use of NIV as an appropriate measure to relief dyspnea due to acute respiratory failure in children with a "do-not-intubate" (DNI) order. A lower proportion, about two thirds of responders, considered NIV appropriate in DNI children with progressive respiratory failure. They considered severity of dyspnea to be the most important indicator to start NIV. The efficacy of provided care was evaluated by clinical measures, the level of attained comfort, and child's and family's satisfaction. Monitoring of gas exchange parameters was only rarely used. Six percent of participants included NIV in their advanced care planning.

In certain instances, decisions on mechanical respiratory support determine the expected disease outcome. The level and modality of provided respiratory support can ultimately preclude the question of life or death. Chatwin et al. (11) reported offering NIV and mechanical insufflation/exsufflation to a group of 13 children with SMA type 1. All the treatment options were discussed with the families. In infants younger than 3 months, NIV was offered primarily as a palliative measure. It was seen that NIV could allow for a successful extubation, eased respiratory symptoms, altered progression of chest deformations and facilitated transfer to the home. The latter was particularly valued by the parents. The authors stressed the importance of the goal-directed approach in palliative NIV for patients with incurable conditions.

Several new therapeutic options have recently reshaped the management of patients with SMA. These possibilities also altered the purpose of NIV in this group of patients. A recent multicenter study addressed the aspects of palliative care in SMA 1 children through parents' reports (12). In the 5 year, observational period (2012–2016), 80 patients from 17 different centers were included, partly in a prospective manner (46%).

In the observed period, seven patients started receiving specific treatment (nusinersen). As expected, survival of patients in the nusinersen group was significantly longer than in non-treated group (57 vs. 1%, $p = 0.001$). Four out of seven patients on nusinersen (57%) were also supported by home NIV, compared to only 8% in the group without specific treatment ($p = 0.006$). Data on care at the time of death were available for the prospectively followed patients only. During the last 48 h before death, 2 children (5%) received NIV. Sedation and analgesia was given to 81% of patients. Pediatric palliative care team was involved in 74% of cases. This article emphasized the importance of the proactive pediatric palliative management in SMA 1 children, the shift of specialized care to the home and consequently even more intensive involvement of the parents.

Palliative NIV is a precious treatment aimed to alleviate berating and thus improve the quality of life. Besides its use in children with NMD, reports indicate positive results in other conditions, too. Bosch-Alcaraz (13) reported on short-term effects of NIV use in 55 pediatric patients managed at a single palliative unit over 7 consecutive months. Large majority of children suffered from NMD (80%), followed by oncological, cardiac, and respiratory illnesses. Silverman Anderson scale was used to grade dyspnea and Edmonton symptom assessment system to evaluate comfort and pain. Over the 24 h observational period dyspnea and pain levels improved in all patients under NIV. Besides, rise in SpO_2/FiO_2 ratio, decrease in heart and respiratory rates were documented. Only minor NIV related complications were noted. NIV provided amelioration and improved comfort in all treated children.

The use of NIV for palliative purposes varies considerably in different societies. Incurable and progressive or static and frail illness often lead to respiratory insufficiency in advanced stages. Girbal et al. (14) retrospectively reviewed characteristics of children with complex obstructive sleep apnea treated with either CPAP or NIV over a 15 year period. Data from 68 pediatric and adolescent patients were analyzed. Participants suffered from congenital malformations/genetic disorders (50%), cerebral palsy (13%), central nervous system tumors (12%), inborn errors of metabolism (9%), and other conditions. Authors reported clinical improvement in 53 compliant children. Improvement in sleep disordered breathing parameters was formally recorded in 29 patients. Although the provided respiratory support could be regarded as a palliative treatment measure in several described children and adolescents, researchers specifically indicated palliative NIV use to improve comfort and decrease hospital stay in four cancer patients.

Optimal care of complex patients requires a holistic consideration of expectations and available management options. A retrospective analysis of 198 children, adolescents, and young adults treated over 32 months at a single specialized pediatric palliative care center (15) revealed high symptom burden in all patient. Distinct symptom clusters were linked to patients in specific TfSL categories (2). Dyspnea was reported as a troublesome symptom in all patient groups except for those in category 1. Overall, patients in category 4 suffered the most pronounced symptoms, especially related to the neurological and respiratory domain. Among the available care tools, presence of a ventilator was reported in up to 30% of patients in category 2.

Nolte-Buchholtz et al. (16) described characteristics of newly referred patients to nine tertiary specialized pediatric palliative home care teams over a period of 6 months. Seventy-five patients with a median age of 7.7 years (range 0–31 years) were included. Twenty-one (28%) were treated for cancer. In the non-cancer group, majority of patients suffered from NMD (52%), followed by neurodegenerative conditions (17%), chromosomal and cardiovascular diseases (11% each). Only one patient had a primarily respiratory disease. In both groups, counseling and symptoms management were offered in over 85% of cases. Overall, compromised communication, pain, swallowing difficulties, and cognitive impairment represented the most troublesome symptoms. Dyspnea was significantly more often expressed by non-oncological patients (50 vs. 19%, $p = 0.019$). Ventilatory support was needed in non-cancer group only; five patients (9%) required NIV, six patients (11%) were ventilated trough tracheostomy. The authors emphasized the medical complexity of the enrolled patients and consequently the need for a committed multidisciplinary palliative care team.

Chatwin et al. (17) analyzed the characteristics of patients who died while receiving long term noninvasive respiratory support at a single large-volume tertiary center. Over an 18 year period, the authors report 109 deaths in 449 patients treated with either NIV or continuous positive airway pressure (CPAP). Seventy-six percent of those who died suffered from NMD. This work was not primarily oriented toward the evaluation of palliative care, but some detailed data were presented for 55 patients. Ten died at the center, palliative extubation was mentioned in one case. Five patents died from expected respiratory failure while on palliative care; four at home, and one in the hospice. The authors specifically stressed the importance of providing palliative care over long time periods with oscillations between active interventions for the management of reversible conditions and times with purely supportive measures.

During the end-of-life phase NIV is reported to improve quality and extent of life. Caregivers perceived improvements in comfort and anxiety relief in patients using NIV at the end of life. Furthermore, this treatment reduced hospital stay. During the last days of life, patients sometimes choose to discontinue NIV or to limit its use and favor the ability to communicate, eat or engage other activities that they consider important (18).

Tolerability may be limited by mask discomfort, discomfort from the air pressure, claustrophobia, poorly managed initial set-up, and child or parent anxiety. The use of NIV can't be designed only to prolong the dying process with no improvement, or possible detriment, to the child's symptom burden and quality of life. Optimal symptom management should relieve suffering and thereby sustain the perceptions of decency in patients and their families during the terminal care.

Presented studies exposed a vast diversity and considerable medical complexity of pediatric patients receiving palliative NIV. Mainly observational evidence supports its ability to

reduce suffering and provide comfort. Nevertheless, a voice of consciousness warns us that mere technicalia should not obscure the principle needs of patients and families coping with unforgiving diseases (19).

Family members have to be involved in palliative NIV decision-making process. They often provide the required every day care and therefore understand the patient's needs at best. Family should be able to dynamically modify therapeutic goals according to the clinical evolution. Clinicians have to respectively consider patients' and families' wishes primarily oriented toward quality of life and dignity (20).

Management of dyspnea is challenging. Several palliative strategies need to be considered in order to attain relief. Patients with dyspnoea can benefit from simple measures to enhance the sensation of air draft. Besides, provision of supplemental oxygen in the cooled airflow further improved the perceived hunger for air (21).

Opioids remain the mainstay to reduce symptomatic dyspnoea and to manage pain. In addition, non-opioid drugs, including local anesthetics, steroids, nonsteroidal anti-inflammatory drugs, acetaminophen, ketamine, and substances with anti—neuropathic action, can be considered. Benzodiazepines are used for sedation of patients with terminal delirium. This condition requires careful assessment. Attention should be paid to known contributing factors like alterations in sleep and other circadian activities (22).

Diuretics significantly help children with fluid retention and dyspnoea associated with pulmonary oedema (9).

ETHICAL DILEMMA

Epidemiological data on long term NIV use in children have identified patient groups that are commonly treated with this respiratory support modality but also point to certain differences. While upper airway obstruction, NMD and pulmonary/chest disorders represent common conditions where NIV is provided, certain reports indicate not infrequent use also in children with cerebral palsy, neurodegenerative disorders, and rare syndromic illnesses (15, 23, 24). Such real-life findings reflect important differences in the management attitudes throughout different societies.

Still, majority of children on long term respiratory support reported leading rich lives. To the contrary, almost one quarter of the caregivers graded the burden of care as severe. Over a half of them suffered from chronic illnesses including anxiety and depression. Providing for a child with such a complex medical condition not infrequently led to family disruptions, single parenting and negative influences on other siblings' lives (25, 26).

Ethical considerations also concern the awareness of the intrinsic level inequality between the patient and family in need of help and the medical team or institution in possession of the means to provide help. Shared decision making should address all positive and negative aspects of the patient's current life condition with special concern to the expected disease course in the future (27).

Technical advancements have made long term respiratory support possible in children with severe chronic health conditions. Moreover, novel therapies and emerging prospects for further expansions in the near future can importantly influence decisions on long term management. Alongside these possibilities it should be recognized that unrealistic expectations might prolong unnecessary suffering and even lead to futile interventions in an individual child.

An ethical framework for decision making in pediatric long term ventilation has been proposed (28). This approach can provide appropriate space for the interaction between the involved patients, their families, healthcare providers, health authorities and the broader society. We believe the patients and families should have the central role in the process, but they need realistic information and appropriate guidance from a dedicated multidisciplinary team (29). The framework should also provide directions on further steps, when consensual decisions could not be reached.

FUTURE DIRECTIONS AND RESEARCH

Current overview exposed paucity of studies addressing the use of NIV in pediatric palliative care. Further research is needed in order to identify benefits and limitations of this treatment modality throughout the vast domain of palliation in children, since NIV has been advocated in the care of various diseases and conditions spanning over long time periods, decisively beyond the narrow frame of terminality. Collaborative multicenter study design, standardized objective evaluations and individual centered research methods should be used to overcome the small number of patients at individual centers, divers, and often descriptive outcomes and single patient and family oriented interventions.

Shifts of established boundaries have exposed important ethical dilemma. An appropriate forum for scientific and public discussion should be made available in order to express doubts, stimulate broad reasoning and thus promote actions in the best interest of all involved.

CONCLUSIONS

NIV should be considered as one of possible options to attain breathing relief in children with either imminent or long lasting life-limiting conditions. However, decisions on any palliative action must follow patients' and families' preferences, perceptions and the relevance of time. A structured professional frameshift should be available for support and ethical guidance in order to provide confidence to patients, families, and all the involved caregivers.

AUTHOR CONTRIBUTIONS

UK drafted, revised, and approved the manuscript. SC revised and approved the manuscript. All authors contributed to the article and approved the submitted version.

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Non-invasive Ventilation and CPAP Failure in Children and Indications for Invasive Ventilation

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Non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) are effective treatments for children with severe sleep disordered breathing (SBD). However, some patients may present too severe SDB that do not respond to NIV/CPAP or insufficient compliance to treatment. A careful revaluation of the interface and of ventilator settings should be performed before considering alternative treatments. In patients with obstructive sleep apnea (OSA), alternatives to CPAP/NIV rely on the underlying disease. Ear-nose-throat (ENT) surgery such as adeno-tonsillectomy (AT), turbinectomy or supraglottoplasty represent an effective treatment in selected patients before starting CPAP/NIV and should be reconsidered in case of CPAP failure. Rapid maxillary expansion (RME) is restricted to children with OSA and a narrow palate who have little adenotonsillar tissue, or for those with residual OSA after AT. Weight loss is the first line therapy for obese children with OSA before starting CPAP and should remain a priority in the long-term. Selected patients may benefit from maxillo-facial surgery such as mandibular distraction osteogenesis (MDO) or from neurosurgery procedures like fronto-facial monobloc advancement. Nasopharyngeal airway (NPA) or high flow nasal cannula (HFNC) may constitute efficient alternatives to CPAP in selected patients. Hypoglossal nerve stimulation has been proposed in children with Down syndrome not tolerant to CPAP. Ultimately, tracheostomy represents the unique alternative in case of failure of all the above-mentioned treatments. All these treatments require a multidisciplinary approach with a personalized treatment tailored on the different diseases and sites of obstruction. In patients with neuromuscular, neurological or lung disorders, non-invasive management in case of NIV failure is more challenging. Diaphragmatic pacing has been proposed for some patients with central congenital hypoventilation syndrome (CCHS) or neurological disorders, however its experience in children is limited. Finally, invasive ventilation via tracheotomy represents again the ultimate alternative for children with severe disease and little or no ventilatory autonomy. However, ethical considerations weighting the efficacy against the burden of this treatment should be discussed before choosing this last option.

Keywords: CPAP (continuous positive air pressure), ENT surgeries, sleep disordered breathing (obstructive/central sleep apnea), NIV failure, educational therapeutic assistance

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INTRODUCTION

Long term non-invasive ventilation (NIV) and continuous positive pressure (CPAP) are increasingly used in children with sleep disordered breathing (SDB) (1–4). The choice of the respiratory support (NIV or CPAP), relies on the underlying physiopathological mechanisms. CPAP is the treatment of choice in severe upper airway obstruction as in obstructive sleep apnea (OSA) (3, 5, 6) or in some cases of lower upper airway involvement as in patients with tracheo or bronchomalacia or bronchopulmonary dysplasia (BPD) (7). NIV represents the first line treatment for chronic respiratory failure associated with neuromuscular disorders (3, 8, 9), central nervous system abnormalities (10, 11), lung diseases (12, 13), chest wall deformities or obesity and hypoventilation (3, 5, 14). Independently from the underlying disease, the aim of the treatment is to normalize overnight and daytime gas exchange and sleep efficiency, improve neurocognitive outcomes, and decrease morbidity and mortality. These benefits may be achieved if NIV or CPAP are able to efficiently counteract the pathological abnormalities responsible of SDB and if treatment adherence is sufficient. Therefore, NIV or CPAP may fail because of a too severe disease or because the child refuses or do not tolerate the NIV/CPAP for a sufficient amount of time.

Alternatives to a non-invasive ventilatory support vary according to the underlying disease severity, the patient's behavioral and cognitive status, the family support and the expected benefit of NIV/CPAP treatment. Treatment options change with child's age and the need for NIV/CPAP requires a constant evaluation. From a practical point of view, treatment failure and therapeutic options must be evaluated in the light of the underlying pathological mechanism and the expected benefit. This review analyzes the current alternative therapeutic options to CPAP and NIV in children with OSA and in children with nocturnal hypoventilation due to neuromuscular, neurological, thoracic, and lung disorders.

OBSTRUCTIVE SLEEP APNEA (OSA)

OSA is defined as the "recurrent partial or complete upper airway obstruction (hypopneas, obstructive or mixed apneas) with disruption of normal oxygenation, ventilation and sleep pattern (15)." The prevalence of OSA in children varies widely from 0.1 to 13% (16). OSA is classically associated with tonsillar hypertrophy in otherwise healthy children, and most of the literature data concerns this population. These children normally have mild to moderate OSA that resolves after adeno-tonsillectomy (AT), and do not require long term CPAP (6, 17, 18). OSA is more common and more severe in children with associated conditions such as congenital craniofacial malformations [e.g., Pierre Robin syndrome (19), complex craniofacial abnormalities (20–22), syndromic craniostenosis (23–25)], metabolic or endocrinology disorders [Prader Willi syndrome (20, 26, 27), storage diseases (21, 28)] or genetic conditions [Down syndrome (22, 29, 30)]. The age of these children with "complex OSA" ranges from newborns to young adults. In children with complex OSA the airway obstruction is most often multifactorial and multilevel requiring an objective assessment and treatment of the different abnormalities that contribute to OSA (31). Moreover, they are also more likely to have persistent OSA after upper airway surgery and represent the large majority of children treated with CPAP (1–3, 5). No data are available in the pediatric population, however the expected benefits of CPAP on nocturnal gas exchange, sleep disruption and cardiovascular outcomes are related to CPAP compliance, with a probable positive dose–effect relationship (32). CPAP should ideally be used during the total physiological sleep time, which may exceed 12 h in infants (e.g., Pierre Robin, Treacher-Collins syndrome). No minimal CPAP/NIV utilization has been validated in children. Some authors propose a minimal use of more than 4 h per night for at least 70% of the nights over a 30 days period (33) while others propose more of 50% of the total sleep time (34). In our center, we recommend an utilization of at least 6 h per night for more than 80% of nights (35).

Checking of Equipment and Educational Support

Objective assessment of CPAP/NIV utilization is mandatory. First of all, in case low adherence, the first step is to check the equipment. **Figure 1** shows a proposed algorithm for alternatives to CPAP/NIV in cases of OSA. As almost all CPAP and NIV devices have built-in software, the first step is to check this data in order to identify possible pitfalls. Device settings must correspond to the prescribed settings. As most of devices have been designed for adult patients, manufactures indicate a minimal weight for correct detection of patients flow. In case of infants, this may underestimate the real use of the device (33, 36). The detailed analysis of the overnight pattern may identify troubleshoot issues like frequent nighttime awakenings or feeding routine in infants (34). Careful evaluation of unintentional leaks should be performed since unintentional leaks may cause conjunctival irritation or excessive mouth dryness. The proper mask fitting should be checked in order to rapidly correct skin injury which is common in infants and children with craniofacial malformations.

The combined analysis of in-built software data and nocturnal pulse oximetry or a sleep study with CPAP/NIV may identify residual respiratory events that require settings changes (35, 37, 38). Autotitrating CPAP may be used as a tool to titrate CPAP level in older children (39). Switch from CPAP to NIV must be considered when high pressures are needed to correct residual obstructive events or if nocturnal hypoventilation persists despite optimal CPAP.

The patient's and caregiver's motivation and support should be assessed if the compliance remains low after checking of all technical issues. Most studies reported a suboptimal compliance with CPAP uses ranging from 4.7 to 5.3 h/night despite a behavioral program and a close follow-up (40, 41). Supportive interventions, educational interventions and behavioral therapy have proven their efficacy to improve CPAP compliance in adult patients (42). To our knowledge, only one study evaluated the effect of educational interventions on CPAP compliance in children, and showed that the benefit of education intervention

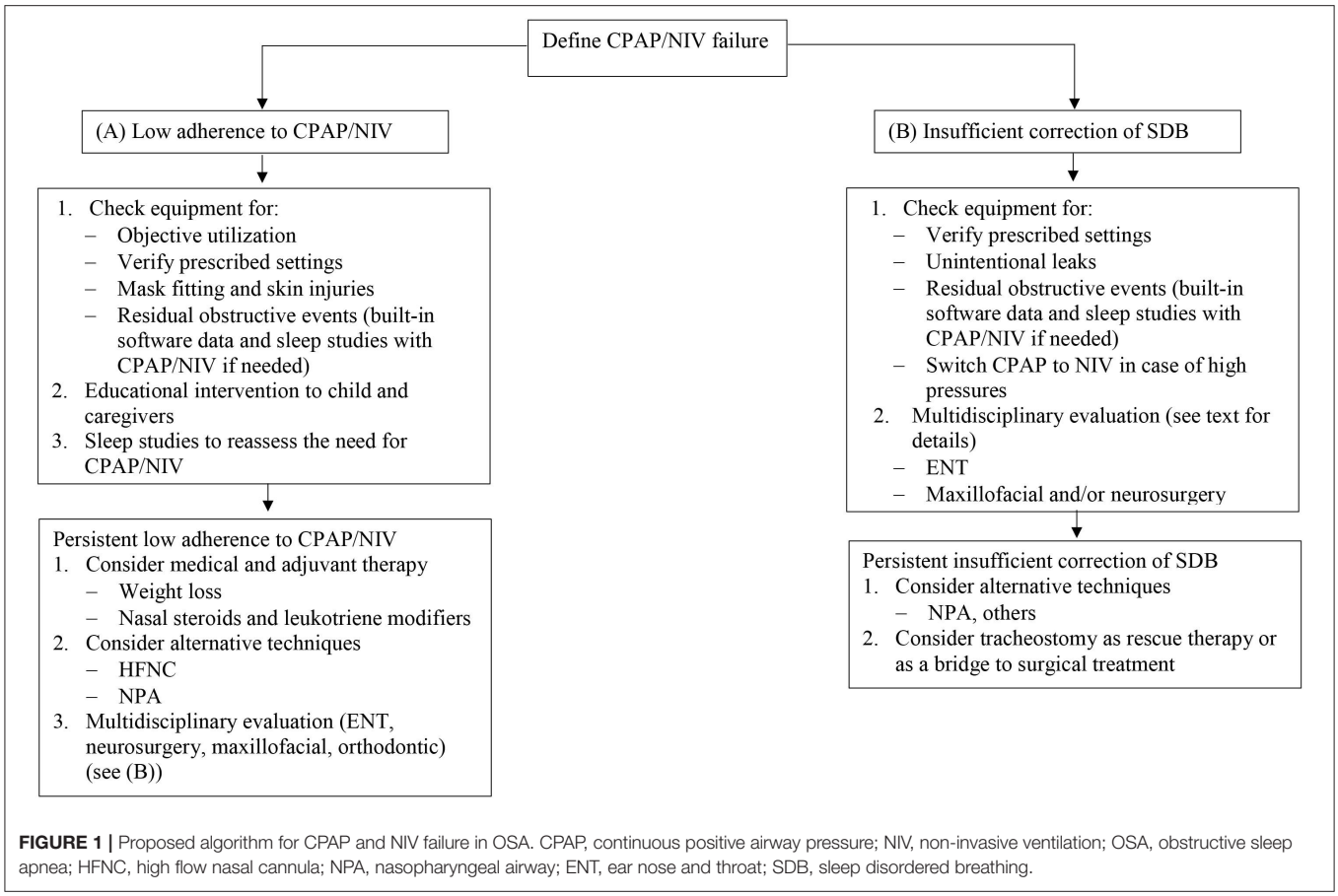

FIGURE 1 | Proposed algorithm for CPAP and NIV failure in OSA. CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; OSA, obstructive sleep apnea; HFNC, high flow nasal cannula; NPA, nasopharyngeal airway; ENT, ear nose and throat; SDB, sleep disordered breathing.

was maintained over time in 3 out of 4 preschool children (43). Importantly, especially for children, it is crucial to choose age- and developmental-adjusted interventions that best match individual patient needs in order to reach the most successful and cost-effective therapy (35). Finally, in those children who have a disease that may improve with age and whose adherence decreases, a sleep study is recommended in order to assess the possibility of CPAP or NIV weaning.

Management of CPAP Failure in OSA

OSA may change with child's growth, with some children improving spontaneously while other deteriorate, justifying a continuous multidisciplinary assessment (44). Despite a high rate of residual OSA after AT, repeated or alternative upper airway surgery in children with craniofacial abnormalities or neurological disorders may cure or improve OSA (45–49). Surgical procedures other than AT may be indicated in children with "complex OSA." In this selected population drug induced sleep endoscopy (DISE) allows the identification of the actual site(s) of obstruction, allowing an optimal individualized treatment (50). Based on the type and site(s) of obstruction, common alternative approaches are turbinectomy, lingual tonsillectomy, supraglottoplasty, uvulopalatopharyngoplasty (UPPP), mandibular distraction osteogenesis (MDO), tongue base procedures, and tongue-lip adhesion. Inferior turbinate hypertrophy (ITH) is a common cause of nasal obstruction in children, especially in those with craniofacial abnormalities. The aim of turbinectomy is to reduce bony turbinate and erectile submucosal tissue while preserving warming and humidification of inspired air. Turbinectomy can be performed at any age and may be associated with adenoidectomy in selected cases depending on patient's anatomical characteristics (51). UPPP is a technique widely used for the management of OSA in adults but not in children. It has mainly been used in children at high risk for persistent upper airway obstruction after AT alone, including children with Down syndrome and neurological disorders (52–54). Potential complications include nasopharyngeal stenosis, palatal incompetence, and speech difficulties. However, the small sample size of the studies, the absence of control groups, and paucity of validated outcome measures preclude any conclusion on the usefulness of this procedure in a broader pediatric population. In children with obesity and Down syndrome, obstruction at the base of tongue is increasingly recognized as a cause of persistent OSA after AT (55–60). Endoscopic-assisted coblation lingual tonsillectomy is effective to treat tongue base collapse in children with OSA (61). Newer techniques like trans oral robotic surgery (TORS) allow an accurate view of lingual base and a better and more efficient dissection of tissues. This may improve the efficacy of the procedure as shown in a retrospective case series of syndromic

and non-syndromic patients with residual OSA after AT or with (CPAP) failure (62).

Rapid maxillary expansion (RME) is an orthodontic treatment that widens the palate and nasal passage, thereby increasing airway caliber and reducing nocturnal upper airway obstruction. The technique can only be used prior to midline fusion of the maxilla, which generally occurs shortly prior to puberty. RME is proposed after the 4th year of life, when the second deciduous molars of the upper jaw have erupted, and the device is usually removed after a period of 12 months (63). RME is restricted to children with OSA and a narrow palate (crossbite) who have little adenotonsillar tissue, or for those with residual OSA after AT. Orthopedic mandibular advancement (OMA) aims to correct dental and skeletal retrognathia by re-directing the mandible into a more forward and downward position. This aims at increasing the opening of the oropharyngeal airway during wake and sleep. Despite its large use in adults as an alternative to CPAP (64, 65) only few studies analyzed the efficacy of this treatment in children. In young adolescents, OMA has been shown to be an effective technique to correct moderate OSA with a mean apnea-hypopnea index (AHI) reduction of 5 events/h (66).

MDO consists in the application of internal or external distraction devices that are placed on each mandibular branch. MDO has been used with success to treat severe OSA due to mandibular hypoplasia, particularly in infants with congenital mandibular hypoplasia such as Pierre Robin sequence or Treacher Collins (67–69). Successful treatment of airway obstruction (defined as either tracheotomy avoidance or decannulation, no need for CPAP, or significant improvement or absence of OSA symptoms) is reported in almost 90% of children by a recent meta-analysis (70). However, rate of post-operative complications is high, with more than 20% of patients having osteomyelitis, epidural abscess, open bite deformity, nerve injuries, or hypertrophic scarring. Little information is available concerning the long term efficacy of MDO performed early in life (71). These data suggest that MDO may be an option for severe OSA in selected patients with mandibular hypoplasia related to congenital craniofacial defects, but the high rate of complications and the possible reoccurrence of OSA limits it use. Other surgical techniques like frontofacial monobloc advancement, or Lefort type 2 or 3 are reserved to congenital facial bone deformities such as faciocraniodysostosis (72–75).

Tracheotomy is an invasive technique that represents the ultimate rescue therapy for children with severe OSA for whom no other therapeutic options are available. On the other hand, in many cases tracheostomy represents a safe and easy to manage therapy. Moreover, practice often depends on local training habits and on the expertise of the different centers, with some team preferring tracheostomy for failure of conservative methods (76). Although tracheotomy is an effective treatment for severe OSA, it may be associated with complications, such scaring, granulous tissue, bleeding, tracheoesophageal fistula, accidental decannulation, tube occlusion or even death, in around 43–77% of children (77, 78). However, some of these complications may be reduced by choosing between the different surgical techniques, or by having particular care in the choice of cannula quality and positioning. Finally, before performing the tracheostomy a complete airway endoscopy is recommended in patients with complex OSA since many of them may present with associated tracheal bronchial malformations that could reduce the efficacy of tracheostomy. Therefore, even if life–saving in some cases, the decision for a tracheotomy should be carefully discussed with a multidisciplinary team, the patient and the parents. It is also important to note that tracheostomy in this setting may be considered as a bridge therapy to lesser invasive methods since most of these children and infants may have a progressive spontaneous improvement of airway obstruction with age or a decrease of OSA severity after surgical treatment allowing a post-operative decannulation (79–81).

Other Therapies

Hypoglossal nerve stimulation is a technique that consists in an implantable device that delivers electrical impulses to tongue protrusor muscles during inspiration aiming at reducing the collapsibility of the upper airway. Hypoglossal nerve stimulation has been shown to be effective in selected adults with OSA and no obesity or circumferential velopharynx collapse (82, 83). This technique has been proposed in some children and adolescents with Down syndrome who had persistent OSA after ENT surgery and who were not adherent to CPAP treatment with a significant improvement in the AHI and quality of life (84, 85), with no surgical complications. However, information on long term follow up is lacking.

Nasopharyngeal airway (NPA) refers to the placement of a modified endotracheal tube in the hypopharynx. In infants with Pierre Robin syndrome or other congenital abnormalities of the upper airway, NPA has shown to be effective and well-tolerated, even if 10–20% of children still require tracheostomy (86–88). The technique is limited to some specialized centers and complications such as displacement of the tube and nostril stenosis have been reported (89).

High flow nasal cannula (HFNC) is a non-invasive ventilatory device that is increasingly used for the treatment of acute and chronic respiratory failure in adults and children (90, 91). HFNC consists of the delivery of high flowing heated and humidified air through the nose, with a fraction of oxygen (FiO_2) that may be set from 21% to nearly 100%. The nasal cannulas used with HFNC are less invasive and more comfortable than nasal masks or nasal prongs used for CPAP therapy. A few case series have reported the use of HFNC in children with OSA (91–93). Our group recently reported the efficacy of HFNC as a rescue therapy for OSA in children and infants non-compliant to CPAP (94). Also, the use of HFNC interface with a modified circuit connected to a standard ventilator has been reported in infants and children not tolerant to CPAP (95).

Some adjuvant therapies may be indicated for selected patients. Weight loss should be the first line therapy for obese children with OSA (6, 15). However, the presumption that weight loss is beneficial in obese children with OSA is based primarily upon evidence from adults. This may be explained by the difficulty to achieve a sufficient weight loss in the large majority of obese children. The few studies that have evaluated the effect of weight loss on OSA in obese children suggested that OSA is likely to improve if a sufficient weight loss is

achieved. Verhulst et al. reported that weight loss was able to improve OSA in 62% of obese teenagers attending a residential treatment center (96). Similar results were reported by Siegfried and colleagues in a similar setting of obese adolescents admitted to a rehabilitation center (97). However, it has to be noted that weight loss achieved in a rehabilitation center may not be extended to home. Moreover, patients with morbid obesity due to some genetical disorders like Prader Willi syndrome or rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation (ROHHAD) weight loss programs are frequently ineffective. For adolescents with morbid obesity and OSA and/or other obesity-associated morbidities, weight loss surgery may be an option (98, 99).

Intranasal corticosteroids or leukotriene modifier therapy have been shown to improve children with mild surgery-naïve OSA or mild residual OSA after AT. This treatment may decrease nasal inflammation and improve nasal obstruction especially in those children with chronic nasal obstruction due to chronic allergic rhinitis or who had difficulties in tolerating CPAP/NIV nasal interfaces.

Positional therapy may be considered when a school-aged child, adolescent, or older teenager presents obstructive respiratory events, occurring exclusively or predominantly in the supine position as compared to the other positions. Several tools such as pillows and belts are commercially available. Positional therapy has not been well-evaluated in children, and a sleep study should be performed to verify its efficacy case per case.

Management of NIV Failure

Hypoventilation, defined by hypercapnia and hypoxemia, is the consequence of an imbalance between respiratory load and the ability of the respiratory muscles to generate an adequate alveolar ventilation (100). Some patients may have clinical unapparent hypoventilation without hypoxemia but others present with associated oxygen desaturations. In these latter the administration of oxygen alone may lead to a worsening of hypoventilation. Since in most of the cases the underlying disorders relies on respiratory muscles weakness or central drive failure, NIV and not CPAP is the treatment of choice to restore normal nocturnal gas exchange. Most of the patients have progressive chronic diseases such as neuromuscular or neurological disorders with little or no improvement over time. This means that, in the majority of cases, NIV represents a long-term treatment and that persistent treatment adherence is of paramount importance. In most of these patients, and in particular in those with neuromuscular disorders, NIV is initially used during the night since nocturnal hypoventilation is the predominant abnormality in the first stages of the disease. In case of low or inadequate adherence to treatment the first step is to check equipment for common pitfalls, as already described for OSA patients. Particular attention should be given to the detection of patient-ventilator asynchronies and unintentional leaks (often mouth leaks), since these represent the most common residual respiratory events in children treated with NIV (101). Then, side effects such as skin injury due to pressure sores, eye irritation due to unintentional air leaks, facial deformity (102) or aerophagia and gastric distension should be looked for and managed promptly. As for patients with OSA, educational interventions and behavioral support should be offered to patients and their families.

Patients with congenital central hypoventilation syndrome (CCHS) and those with spinal cord injury and elective diaphragm palsy may be eligible for diaphragm pacing (DP). DP consists on an implantable device that sends electrical impulses to the diaphragm via the phrenic nerve. Successful decannulation and management of SDB in pediatric CCHS patients have been reported, even though treatment efficacy should be carefully assessed because this approach may not be sufficient or cause obstructive respiratory events (103, 104).

Finally, when respiratory insufficiency progress, especially in children with advanced neuromuscular disease, NIV may fail to guarantee efficient correction of nocturnal and daytime gas exchange. Some groups reported successful experience with NIV in totally ventilator-dependent children with neuromuscular disease (105), while others consider that a minimal time per day of spontaneous breathing is needed in order to balance medical benefit and quality of life of the child and his family (106). In this case invasive ventilation (IV), may represent an alternative to NIV although it represents an option which has to be prepared and discussed thoroughly with the child and his parents (107). In children with a severe underlying disease with a rapidly fatal outcome, developmental delay or severe physical or cognitive disabilities tracheostomy may be even more controversial since the transition from NIV to IV may be associated with a too high burden with regard to the improvement in quality of life of the child and his family (108).

CONCLUSION

CPAP and NIV are widely used to treat SDB in infants and children. However, their efficacy depends on treatment adherence and underlying diseases severity. Checking of equipment and patient's and caregiver's education are of paramount importance to achieve an optimal CPAP/NIV use. For patients with OSA and CPAP failure, a multidisciplinary approach is recommended in order to choose the most appropriate therapeutic option. In patients with nocturnal hypoventilation due to neuromuscular or neurological conditions, the range of alternative therapies is limited. Tracheostomy with or without invasive ventilation represents an option that need to be discussed with the patients and families, and ethical considerations weighting the efficacy against the burden of this treatment should be discussed.

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AA is the main author of the manuscript. BF, SK, LG, TT, and AL contributed to the conception of the manuscript. All authors approved the final version of the manuscript.

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REVIEW
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Transition to Adult Care in Children on Long-Term Ventilation

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The number of children on long-term ventilation (LTV) has exponentially increased over the past few decades. Improvements in management of ventilation coupled with improvements in standards of medical care are increasingly allowing young people on LTV to survive into adulthood. The process of transition from the pediatric to the adult healthcare system is challenging and requires special attention.

This review aims to provide an overview on transition to adult care for children on LTV. Firstly, examining effective models of transition in other childhood onset chronic conditions as a template, whilst highlighting the unique aspects of transition in LTV patients and secondly, summarizing the main relevant findings in the literature on the topic and emphasizing the importance of a multidisciplinary approach to this process.

Keywords: transition, pediatric to adult services, long term ventilation, barriers and facilitators, Home mechanical ventilation

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INTRODUCTION

Improving medical care has resulted in a progressive increase in the number of children with chronic diseases reaching adulthood and more than 85% of children with chronic illness now will need to transition to adult services. These patients can be broadly stratified according to their level of need: ∼5% have complex needs; 25% have complex chronic conditions; whilst the remaining 70% are patients with chronic conditions with good control (1). Children on LTV tend to fall into the first two categories. Since the initial use of LTV in children to treat chronic respiratory failure in the 1980s, its use has expanded and it is now widely used in three main scenarios: neuromuscular disease, upper airway conditions, and abnormalities of central respiratory drive, e.g., congenital central hypoventilation syndrome (2, 3). LTV is effective in improving respiratory parameters and thoraco-abdominal coordination during sleep, reduces the workload of the respiratory system, palliates symptoms, and in certain conditions, has been shown to increase life expectancy (4–7). More widespread provision of LTV support, in conjunction with improved survival means that increasing numbers of patients on LTV will be transitioning to adult services.

This process of transition from pediatric to adult healthcare systems is one of the most challenging periods for patients. Blum et al. (8) defined "transitional care" as "the purposeful, planned movement of adolescents, and young adults with chronic physical and medical conditions from child-centered to adult-oriented healthcare systems". Adolescence is recognized as a vulnerable period due to the physiological, emotional, and psychosocial changes occurring. Adolescents with chronic diseases not only have to deal with the problems and needs that healthy adolescents have, such as the need to make new friends and form close relationships, school

struggles, new intellectual interests, physical, and sexual attractiveness, setting of goals and future objectives; they similarly face choices about risky behaviors (alcohol, tobacco, and drugs) whilst facing the potential for greater adverse health outcomes from these behaviors (9). Therefore, it is essential to consider "transition" from pediatric to adult services in the global context of a period of multifactorial change for the patient.

Most healthcare professionals are trained in either pediatric or adult medicine and often feel less confident when managing adolescents (10). An international cross-jurisdictional policy scoping review by Hepburn et al. (11) examined all publicly available national government documents detailing transition strategies, from nine countries with comparable healthcare systems. They found that transition has received little government attention and only two of the nine countries had an operational strategy regarding transition. Whilst many hospitals have developed transition programs, most are institution and disease specific and not universally accessible (11). They are also often limited in terms of capacity and face funding barriers.

Doing transition well, is arguably even more important for patients with complex diseases, such as those on LTV, however, it is also in these very patients where inadequacy of transitional care is more evident. It is instructive to examine the current differing care models that already exist for the transition process, for different chronic pediatric diseases to see what is applicable to patients on LTV.

CONGENITAL HEART DISEASE

Advances in management of congenital heart disease (CHD) have resulted in a significant improvement in survival, particularly in those with more complex conditions (12). Almost all international guidelines on the care of CHD patients now include recommendations regarding transition. The lack of adult specialists and of adequate facilities in adult hospitals for patients with CHD has been highlighted as an issue. Infrastructure and staff requirements for specialist "grown up CHD" centers have been defined (13). Specific formal training in the subspeciality has been identified as being essential for adult and pediatric cardiologists. European guidelines advocate at least one assessment in a specialist center where the CHD specialist can assess the required level of care and frequency of follow-up, stratifying patients to those requiring continued specialist follow up, those who can have shared care with general adult cardiac services, and those who can be managed in general (non-specialist) cardiac clinics, with access to specialist care when required (13). American guidelines highlight the importance of delivering developmentally appropriate transition education to teach patients and families about the expectations and concerns regarding their specific CHD condition, as well as the skills to navigate the adult healthcare system (14). A trial of a transition intervention consisting of a 1 h nurse-led one-on-one teaching session resulted in significant improvement in cardiac knowledge and self-management scores 6 months post-intervention (15).

CYSTIC FIBROSIS

Considerable investment in clinical and basic science research has transformed cystic fibrosis (CF) from an early lethal condition to a chronic illness. Mathematical modeling of UK CF registry survival data predicts that over half of babies born today, can expect to survive into their fifth decade, if not longer (16). The period of transition to adult care is a crucial time in the natural history of CF patients. Late CF related complications such as infertility, gastro-intestinal cancer, and infections by multi drug resistant pathogens such as atypical Mycobacterium, have emerged. Psychological issues associated with worsening lung function, reduced life expectancy, and diminished fertility may manifest and adolescents may be influenced by peers to try risky behaviors such as smoking which could have a significant detrimental impact on their lung function (17). The response of the CF community to these challenges has been commendable. Strong advocacy and emphasis on research into health care transition have meant that CF services now offer one of the highest quality transition processes amongst all the chronic diseases and there is much one can learn from them (18). North American and European standards of care and consensus guidelines for the care of CF patients include recommendations on transition (19–21). Some features highlighted include:

(a) Starting discussions about transition early.
(b) To aim for patient transfer to occur between the ages of 16–18 years, but this should incorporate a degree of flexibility, reflecting the patient's developmental maturity, and health status.
(c) The need for close cooperation between the pediatric and adult centers, with continuity of care being facilitated by the joint adoption of the same diagnostic and treatment protocols tailored to specific age groups.
(d) A formal transition clinic where there is participation of both pediatric and adult teams.
(e) Referral only by letter is suboptimal.
(f) A comprehensive formalized transfer report including input from every member of the multidisciplinary team must be provided.

TYPE 1 DIABETES MELLITUS

Unlike CHD and CF, survival into adulthood has not in the main been an issue in Type 1 Diabetes Mellitus (T1DM) meaning its transition processes are some of the most well established. Alassaf et al. (22) found that young persons with complicated health histories and less education are more likely to have poorer diabetic outcomes following transition to adult care. Different models of transition such as having specific young adult clinics, a dedicated transition co-ordinator and structured transition program, and giving the opportunity for patients to get to know the adult health care providers have all shown good results (23). Overall, when young adults are supported during the transition period, clinic attendance, and glycemic control can be maintained or improved, and diabetes-related complications reduced (23).

Whilst much can be learnt from established transition models, the advent of better personal communication technology affords the potential for new paradigms to enable transition. Results from a randomized clinical trial evaluating an 8-month technology based transition intervention MD2Me has had promising results in a mixture of patients with CF, T1D, and inflammatory bowel disease (24). The focus was on generic disease management skills rather than disease specific skills, with 81 patients recruited and randomized to receive standard care or MD2Me. The intervention arm consisted of a 2-month intensive web-based and text-delivered disease management and skill-based intervention followed by a 6-month review period. Participants also had access to an automated SMS algorithm that provided disease management decision support and was a communication portal with the health care team. MD2Me patients showed significant improvements in performance of disease management tasks, health-related self-efficacy, and patient-initiated communications compared with controls. Technology based interventions may be particularly relevant to patients on LTV, given that the majority of ventilators now have the capability to remotely transmit ventilator data to the clinical team and clinicians can also remotely adjust ventilatory settings.

UNIQUE ASPECTS OF LTV PATIENTS

As mentioned earlier, LTV patients tend to be patients with complex needs. A large proportion are patients with NMD who are often transitioning at a time when natural disease progression is resulting in loss of independence, an increasing reliance on LTV, and the emergence of a raft of new health problems. A survey of patients with Duchenne muscular dystrophy (DMD) and their families regarding transition found that approximately a third of the young men in the study were not in any kind of education, training, or work (25). The majority thought they were unlikely to get jobs and those who had tried, reported facing insurmountable difficulties relating to employer attitudes, access problems, and a lack of specialist advice regarding employment. A smooth transition is crucial for both their physical and psychological health. It is not just the mental health of patients at stake. Eighty percent of the parents of these young adults reported clinical levels of depression and anxiety. They felt that appointments in later childhood and early adulthood seemed to focus on charting the decline and deterioration of the health of the young men with DMD, something both parents and patients found to be a deflating and demotivating experience. However, issues such as ceilings of care and views regarding tracheostomy insertion do need to be explored and the balancing of these contrasting needs is difficult and requires both experience and adequate resources.

Another group of patients are those with severe cerebral palsy, who are on LTV for nocturnal hypoventilation. They may have severe neurocognitive impairment, seizures, and often require gastrostomy feeding. Given these needs, they are often heavily/completely reliant on their parents for their cares. This does not easily fit into the typical model of adult health care where there are expectations that it is the patient who directs and is responsible for their own care. Given the diversity of diseases that are now benefiting from LTV, the individual differences in disease progression between patients and the variations in both local and national care provision, transition for LTV patients cannot be a one size fits all approach, but needs ideally to be realized on an individual basis.

TRANSITION IN LTV PATIENTS—CURRENT SITUATION

In 2011, the American Academy of Pediatrics (AAP) published a clinical report on supporting the health care transition (HCT) from adolescence to adulthood in the medical home (26). It proposed an algorithm containing action steps such as discussion of transition policy, initiation of a transition plan, and review of this plan at specific time points. It incorporated an assessment of transition readiness—this assessed the skills the adolescent would need to acquire in preparation for the change from pediatric parent supervised health care to patient centered adult health care with the legal assumption of self-determination at age 18 years. It also highlighted the importance of clarifying issues such as medical decision-making responsibilities and adult consent and confidentiality policies. On the back of this report, the "Six core elements of health care transition," a structured process that can be customized for use in different settings and applied to different types of transition care models was developed. The six sequential core elements are:

1) Discussion of transition policy
2) Transition tracking and monitoring
3) Transition readiness and/or orientation to adult practice
4) Transition planning
5) Transfer of care
6) Transition completion and ongoing care with the adult healthcare team.

Similarly, the Canadian Thoracic Society have published clinical practice guidelines on pediatric home mechanical ventilation and the recommendations they made regarding transition are summarized in **Table 1** (27).

Despite this, when pediatric pulmonary program directors in the US were surveyed on the transition process of their respiratory technology dependent patients in 2015, 78.1% of respondents reported their work place did not use a standard protocol for transition, of which 41.4% had no process in place at all, only 13.8% assessed transition readiness and only 24% track the transition process until the first visit with the adult team (28). These results revealed just how much progress still needs to be made in this group of patients.

FACILITATORS AND BARRIERS TO TRANSITION FOR LTV PATIENTS

Dale et al.'s (29) recent qualitative research explored the transition experience of patients who had undergone the home mechanical ventilation (HMV) transition program of a tertiary children's hospital to their partnering adult hospital. Identified factors that aided transition include early transition discussion,

TABLE 1 | Recommendations for transition of patients on LTV.

1. Transition is an ongoing process and planning should start early in childhood.
   a. The adolescent and his/her caregivers should have a good understanding of his/her medical condition and what is required for transition into the adult healthcare system. If feasible, based on the developmental level of the child, the patient should be involved in planning discussions in a way that is meaningful to them.
   b. The adolescent should be involved in planning discussions and assume the management of their condition to the extent that they are able, prior to transfer of care.
   c. Providers should facilitate and encourage the attainment of self-esteem and self-confidence to allow successful transition and assumption of as much independence as their condition allows.
2. A formalized approach to transition is needed
   a. A formal transition plan should be developed in collaboration with the adolescent and his/her family.
   b. The transition program should be agreed upon and coordinated by both the pediatric and adult healthcare teams.
   c. Joint transition clinics with the pediatric and adult healthcare teams are recommended.
3. Should the adolescent be unable to provide informed consent, discussions regarding whom should have this responsibility need to be clarified. Conversations regarding goals and ceilings of care should be had with the pediatric team and the details of these conversations need to be clearly communicated to the adult healthcare providers.
4. Any differences in care in the adult setting from their usual pediatric care, need to be highlighted. The adolescent and his/her caregivers need to be made aware of any changes to homecare support.
5. A named key worker to oversee and co-ordinate transition support, help the young person navigate adult services, be the link between them, and the various practitioners involved in their support, advocating for them when necessary, can be invaluable.

Adapted from Ian MacLusky and Krista Keilty on behalf of the CTS Pediatric Home Ventilation Guidelines Panel. Section 12: Transition from pediatric to adult care. Can J Res Crit Care Sleep Med. (2018) 2(Suppl 1):83–7. doi: 10.1080/24745332.2018.1494992.

joint pediatric—adult HMV clinic visits, written information about adult services, and communication training for the adolescents to improve their capacity to give accurate medical histories and discussions of their needs with the clinical team. The barriers identified include lack of referral to other medical specialists, difficulty co-ordinating appointments across multiple adult specialists, and health care settings, inadequate information on adult community funding structures, and limited involvement of family doctors. The next section explores these barriers in more detail.

CARE DELIVERY AND CO-ORDINATION

In some countries, one of the most significant barriers is the lack of adult health care teams to whom LTV patients can be transitioned to. Similar to the situation in CF a few decades ago, only a limited number of adult physicians have experience in looking after these patients and the multidisciplinary team set up which patients and their families are used to in pediatric care may only exist in a few tertiary centers. Some pediatric teams are therefore having to continue to look after these patients well into adulthood (30). Development of these adult services and training of the next generation of health care professionals needs to be a priority. From the CF experience, we know that it is possible to rise to this challenge—when the CF Foundation in the United States mandated that approved CF programs must provide adult CF services by the year 2000, it galvanized rapid progress and development of adult CF service provision to the high standards achieved now. It must be cautioned though, that the relative rarity of some diseases of patients requiring LTV makes the advocacy that CF relied on potentially less potent. Thus the potential unification of multiple small patient advocacy groups to address this must be considered.

In addition to being under the care of the pediatric pulmonologist who manages the respiratory and LTV aspects of his/her care, patients are often also under the care of several other specialties. For example, a neuromuscular patient will also typically be under the care of the neuromuscular pediatrician, spinal surgeons for scoliosis, orthopedic surgeons if they have dislocated hips, and may also see a cardiologist if their condition is associated with cardiomyopathy, gastroenterologist, or urologist. The transfer to the respective adult clinicians ideally should be done sequentially rather than all at the same time and thus requires careful advance planning. Feedback from our patients suggests that they appreciate having input into their sequence of transfer of care, often preferring transfer of services which were least engaged first, followed by the more closely involved services, often choosing to transition from respiratory LTV services last. Some adult centers are learning from the pediatric model and have started to develop "one stop" multidisciplinary services where patients are not only seen by the LTV team, but also in conjunction with neurology, orthopedics, gastroenterology, cardiology, and urology as required. This will help considerably with the problem of fragmentation of subspecialist input.

In certain health care systems, there may also be insurance coverage and cost of care barriers. For example in the US, pediatric hospitals may not always participate in the same medical insurance plans as their partnering adult hospitals. Patients would then have to face the choice of changing insurance providers, with the attendant changes to durable medical equipment, nursing, and pharmacy services, or stay with the same insurance company, but transition to another adult hospital covered by the insurance plan, which might not

have the optimal pulmonary expertise or as close links with the pediatric team.

Transfer to adult care is best conducted when the youth's health condition is stable. Some adolescents on LTV are amongst the most vulnerable patients and may have periods with frequent or prolonged hospitalizations which can delay transition. It is therefore important to factor in unexpected, unavoidable delays, and not leave transition to the last minute. Pediatric wards and pediatric intensive care units often have age cut offs above which they will not accept a patient and should the young person become unwell and require an acute admission, being admitted to an adult ward without having completed the transition process is less than ideal.

PATIENT PREPARATION AND ENGAGEMENT

Preparation for transition needs to occur early on—as adolescence approaches, developmentally appropriate education needs to be integrated into the patient's care plan, to better enable their understanding of their medical condition, and encourage more active participation and gradual assumption of responsibility for their medical care. Adolescence is a time when health is often not on the list of top priorities for a young person. When starting college and making new friends, remembering to change the filter on one's ventilator, and getting it serviced can easily be forgotten.

If available, having a designated adolescent ward or clinic can be a helpful stepping stone towards integration into adult services. Adolescent patients can feel they "don't fit in" if admitted to the same ward as a 70 year old on LTV for chronic obstructive pulmonary disease. Recent feedback from one family stated their teenage son was incredibly upset after attending an adult clinic as whilst waiting to be seen, they met an older patient with the same underlying condition, who had significantly more morbidity, being much weaker, and needing ventilation via a mouthpiece during the day as well as overnight. Woken to the potential ramifications of his condition, he struggled to come to terms with this, eventually needing referral for psychological support.

Over the years, these young people and their families have built up relationships with the nursing staff, clinicians, and health care professionals. It can emotionally be very difficult to break off contact and learn to trust a new set of clinicians. Young people and their careers have also become very familiar with the routines in clinic and on the ward and know how to access the various services available. Getting to know a new adult health care system can be challenging, and even simple logistical issues such as arranging transport to attend hospital appointments may not be straightforward when one is non-ambulant, given the attendant need for multiple equipment such as ventilators, cough assist, and suction machines, as well as feed pumps. Having a named key worker to oversee and co-ordinate transition support, help the young person navigate adult services, be the link between them, and the various practitioners involved in their support, advocating for them when necessary, can be invaluable.

Any differences in organization, investigations, and treatment between the pediatric and the adult center should be clearly documented and explained to the patient before transition. The adult team may use slightly different medications or therapies and some practices may vary. This needs to be clearly explained to families so they know what to expect, and applies to all aspects of the multidisciplinary care. Ceilings of care and healthcare expectations should be discussed during transition and revisited—the young person should be reassured that just because they have made a certain decision at this point in time, circumstances may change and they can change their mind in the future.

When handing over to the adult team, in addition to medical details such as ventilator settings, medications, and sleep study results, patients often appreciate it when the adult team are interested in getting to know them as a person as well. This is reflected in the transition paperwork from our center by a section titled "All about me," where the young person writes down the things which they feel are important for the adult team to know about them. This has proved to be very helpful because it can stimulate topics of discussion when patients first meet the adult team, which can break the ice and help establish a good rapport.

TABLE 2 | What can we learn from the transition experiences of other medical conditions?

(1) No one transition model has been shown to be clearly superior to the rest. Adopting the model that best fits with how local healthcare is organized, whilst bearing in mind the recommendations in **Table 1** seems a pragmatic option.
(2) Formal training in transition should be part of the training of pediatric and adult physicians.
(3) Investment of time and resources into patient education can improve understanding of their medical condition and facilitate development of self-efficacy.
(4) Strong advocacy can result in rapid progress and development of high quality adult multidisciplinary teams and transition services.
(5) Discussions about transition should be started early.
(6) There needs to be close cooperation between the pediatric and adult centers, ideally with joint adoption of the same diagnostic and treatment protocols tailored to specific age groups, to ensure a transition that is as seamless as possible.
(7) A formal transition clinic where there is participation of both pediatric and adult teams is important.
(8) A comprehensive formalized transfer report including input from every member of the multidisciplinary team must be provided.
(9) With adequate support during the transition period, clinic attendance and health can be maintained. A named key worker to oversee, coordinate, or deliver transition support, and be the link between the young person and the various practitioners involved can be very helpful.
(10) Technology based interventions may be a helpful adjunct, especially since the majority of ventilators now have the capability to remotely transmit ventilator data to the clinical team and clinicians can also remotely adjust ventilatory settings.

"SOCIAL" ASPECTS OF TRANSITION

While the clinical complexities of patients are often the predominant focus for medical personnel, these should not overshadow the "social" aspects of transition. These are slightly outside the remit of this review, but the experience of those undergoing transition in cerebral palsy (CP) is salutary in this regard. For in CP, the primary barriers to transition identified have been the navigation of the complex systems of services and supports, the lack of information and resources, and finally societal prejudices and stigmas toward individuals with disability (31–33). The parallel for LTV patients is obvious, with examples including the financial implications of the potential transfer of funding from the parents directly to the patient. Similarly, receiving educational institutions/employers often require clear guidance on the patient's functional capacity and degree of technology dependence to ensure that this can safely be accommodated. Sadly, employers or tertiary institutions are often initially reluctant to address these demands despite clear regulatory requirements. It has been our experience that patient support groups and charities can often be incredibly helpful in bridging the gaps in understanding seen in the wider non-medical context of further education/employment. Their role as a source of specific relevant information and capacity to facilitate communication often makes them invaluable partners for patients and medical teams during and after transition. For example, in the UK, Action Duchenne ran a Transition to Adulthood project providing information for patients regarding further education, training, and/or employment options, independent living including housing options, the impact of good health care provision including the importance of advice on sexuality, health, and relationships. Contact for families with disabled children provides parents with information such as on the UK Care Act 2014, explaining the important legal duties on local authorities about what must happen when a child makes the transition from children's to adult services and the rights of the young persons and careers. The majority of organizations also have a helpline for advice where workers already known to families can provide support with no predetermined age cut off. The key to the best utilization of these NGOs from a medical perspective is the realization of their existence, so suitable sign posting, if agreeable to the patient/family, can allow the development of a working relationship prior to transition. Parent/careers are also often reaching an age where they may themselves have health issues and may not be able to care for the patient in the same way as before and the familiarity of people whom they perceive have the long term interests of the family at heart can be of great benefit. Special mention should also be made regarding patients who are under the care of social services and/or those who lack the capacity for autonomous decision making, as the issue of power of attorney needs to be addressed before transition can be completed. The ultimate holy grail is a holistic approach to transition where preparation for transition meetings ideally should also include wider community agencies such as community health teams, education, and social services.

FUTURE RESEARCH

When the AAP transition guidelines were updated in 2018, new recommendations pertaining to research were added (34). These highlighted the importance of developing a stronger evidence base, examining transition outcomes in terms of population health, patient and family experience, healthcare use, and cost savings. Using a three stage Delphi process, members of the Health Care Transition Research Consortium identified the top 10 health care transition outcomes of adolescents with special healthcare needs (35). Quality of life was rated the most highly. The others included understanding the medical condition and its complications, knowledge of medications, self-management, adherence, understanding health insurance, attendance at medical appointments, having a medical home, avoidance of unnecessary hospitalization, and having a social network. Achieving consensus is an important first step toward high quality transition research and thus it is hoped that this ranking will help provide a framework for future research on transition programs for LTV patients.

CONCLUSION

While transition services for LTV patients are, for the most part, often still in their infancy, there are some obvious themes already emerging. The most important of these is that done effectively, transition is a process, not a single event of transference of care. The insights gained from examination of other chronic diseases (summarized in **Table 2**) highlight the absolute requirements, where possible, for better education and communication. The later not only reflecting the conversations between medical professionals and patients, but also between the pediatric and adult teams involved in planning and coordinating this process. Strong advocacy from both patient groups and medical professionals is needed to stimulate the system wide changes still very evidently required. Key amongst these from a systemic medical perspective is the widespread establishment of multidisciplinary adult healthcare teams and the training of the next generation of health care professionals experienced in looking after patients on LTV. For although all patients, whether manifesting complex needs or not, require some degree of individualized planning, this can only happen if there is a systemic recognition of the need for greater collaborative care partnerships between pediatric and adult clinicians.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

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frontiers in Pediatrics

ORIGINAL RESEARCH
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Evolution of Pediatric Home Mechanical Ventilation Program in Serbia—What Has Changed in the Last Decade

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Home mechanical ventilation (HMV) is a method of treatment in children with sleep-disordered breathing (SDB) and alveolar hypoventilation regardless of primary disease. The goal of the study was to describe the changes in the HMV program in Serbia during the last two decades. Cross-sectional retrospective study included data from the national HMV database from 2001 until 2019. HMV was initiated in clinically stable patients after the failure to wean from mechanical ventilation succeeded acute respiratory deterioration or electively after the confirmation of SDB and alveolar hypoventilation by sleep study or continuous transcutaneous capnometry and oximetry. The study included 105 patients (50 ventilated noninvasively and 55 ventilated invasively via tracheostomy). The median age at the time of HMV initiation was 6.2 years (range: 0.3–18 years). Invasive ventilation had been initiated significantly earlier than noninvasive ventilation (NIV) ($p < 0.01$), without difference in duration of ventilatory support ($p = 0.95$). Patients on NIV were significantly older ($p < 0.01$) than those ventilated invasively (13 and 1.5 years, respectively). Average waiting time on equipment had been shortened significantly—from 6.3 months until 2010 to 1 month at the end of the study ($p < 0.01$). Only 6.6% of patients had obstructive sleep apnea syndrome (OSAS) requiring HMV. During the study period, 24% patients died, mostly due to uncontrolled infection or progression of underlying disease. Availability and shortened waiting time for the equipment accompanied by advanced overall health care led to substantial improvements in the national HMV program. However, future improvements should be directed to systematic evaluation of SDB in patients with OSAS, early diagnosis of nocturnal hypoventilation, and subsequent timely initiation of chronic ventilation.

Keywords: home mechanical ventilation, non-invasive ventilation, tracheostomy, chronic respiratory failure, alveolar hypoventilation, obstructive sleep apnea

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INTRODUCTION

Mechanical ventilation at home (HMV) is a recognized method for the treatment of the sleep-disordered breathing (SDB) and alveolar hypoventilation in childhood. The population of children requiring HMV is growing rapidly worldwide, mostly as a consequence of advanced life support for technology-dependent patients and early recognition of alveolar hypoventilation (1, 2). Despite the significant financial burden on the health care system,

initiation of HMV has hugely facilitated health care of these patients. Besides the obvious benefits such as life expectancy, many studies confirmed that HMV enhanced quality of life, and social interactions, along with decelerating lung function decline and improving nutritional status (3, 4). In some patients, however, HMV caused procedure-related complications (e.g., midfacial hypoplasia and malocclusion) (1, 2).

Even though the HMV trend began in high-income countries, the last decade showed that well-organized respiratory units in referral hospitals from low- and middle-income countries were capable of implementing adequate national HMV programs (5–10). The first national survey on HMV in developing countries, particularly in Serbia, was published almost a decade ago (11), following which the number of patients has increased remarkably.

The primary goal of this study was to outline the changes in the last decade regarding clinical practice and the obstacles for adoption and implementation of the HMV program in our system with limited resources. In addition, we speculated that delayed initiation of HMV and non-existence of home-care providers resulted in higher prevalence of invasively ventilated children.

MATERIALS AND METHODS

In a relatively small country such as Serbia, with seven million inhabitants (2.8 million being younger than 18 years of age), there are five university children's hospitals. The Mother and Child Health Care Institute is a multidisciplinary pediatric center and the only national HMV center. According to the national health care policy, the decision for initiation of HMV should be made in the Institute, based on careful evaluation of the medical records, patient's clinical status, and the results of diagnostic procedures.

This cross-sectional study included retrospectively evaluated medical records extracted from the Serbian national HMV database, collected from 2001 until September 2019. Data included patient demographics, underlying disease, and criteria for HMV initiation in patients who had been ventilated at home for a period of at least 3 months. Finally, the outcome was recorded—duration of HMV and reason for its termination. The study protocol was approved by the local ethics committee (decision number 8/3).

Criteria for Initiation of HMV

The primary indication for initiation of HMV was hypercapnic respiratory failure, documented by increased $PaCO_2$. Many patients had HMV started after an acute respiratory event and subsequent weaning failure, while in other cases, a sleep study was performed to document SDB. During the last 5 years, HMV was started electively after confirmation of nocturnal hypoventilation that precedes chronic respiratory failure (CRF).

Clinical tests of respiratory function with the comparison of the obtained results and monitoring of its values in order to detect potential declines were performed in patients with neuromuscular disorders (NMDs) in whom the test was possible. Peak cough flow, spirometry, and respiratory muscle strength measurements were obtained in patients who were cooperative during the procedures. Although these tests are not precisely validated, significant negative trends or low absolute values (peak cough flow $<$ 160 L/min, forced vital capacity $<$ 70% predicted, maximal inspiratory pressure $<$ -60 cmH_2O, or sniff nasal inspiratory pressure $<$ 40 cmH_2O) led to further evaluation of nocturnal hypoventilation. Right from the national HMV program initiation, diagnostic polygraphy was used as a screening test in patients with NMD, and all patients with a suspected OSAS apnea–hypopnea index (AHI) of $>$5 episodes h^{-1} were confirmed to have SDB. In addition, until 2015, continuous pulse oximetry followed by arterial blood gases analysis (ABG) after awakening was performed. From 2015 onward, diagnostic evaluation was upgraded by overnight gas exchange estimation when the equipment for continuous transcutaneous capnometry ($PtcCO_2$) and oximetry became available (12). More than 2% of total sleep time (TST) with SpO_2 $<$ 90% or $>$2% of TST with $PtcCO_2$ $>$ 50 mmHg was consistent with findings of nocturnal hypoventilation (13).

Further treatment depended on primary etiology or diagnostic group. Patients with SDB and OSAS, due to upper airway obstruction, were started on continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). Patients with CRF were started on either chronic invasive ventilation or non-invasive ventilation (NIV). Our multidisciplinary team discussed every case and prescribed further treatment. Taking into consideration the objective criteria and psychosocial circumstances, each patient and his/her family was evaluated very carefully, and patients motivated and capable of starting with HMV gave their written informed consent.

For NMD patients who needed ventilation 24 h a day, either Vivo 50® (Breas) or Trilogy 100® (Respironics) ventilators were recommended. In most of these patients, tracheostomy was performed due to bulbar symptoms or weaning failure in intensive care unit (ICU). For those patients who did not require continuous ventilation, Vivo 40® (Breas) or A 40® (Respironics) ventilators had been used mostly. CPAP devices were recommended in all patients with OSAS and documented SDB. Eligible patients and their families were advised to start HMV regardless of the recommended list of indications covered by the health care system reimbursement policy. Costs of equipment were covered by parents, charities, or the national health insurance fund. When necessary, cough-assist machines were also bought by patients on their own. In majority of cases, caregivers had been the patient's parents or relatives.

Statistical Analyses

Statistical data were analyzed by IBM SPSS Statistics 25 for Windows and are expressed as median and range. Differences in medians between non-normally distributed variables were analyzed by Kruskal–Wallis and Mann–Whitney *U*-test. Differences between categorical variables were tested using chi-square and Fisher's exact test. Correlations were evaluated by Spearman's rank correlation test. Statistically significant differences were documented by $p < 0.05$.

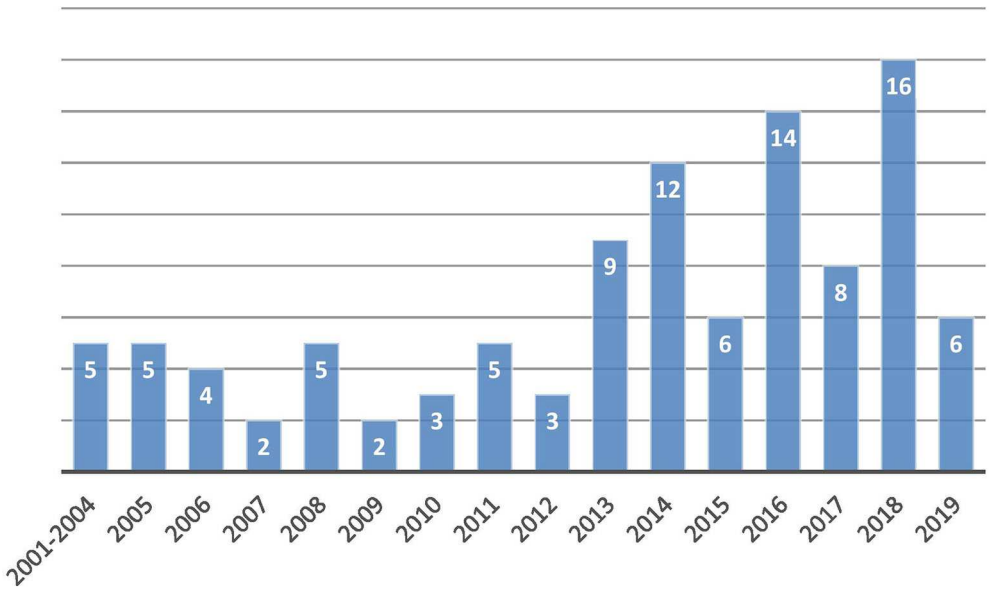

FIGURE 1 | Number of new patients per year.

RESULTS

Patient's Characteristics

Since 2001, the number of patients has increased steeply, particularly during the last 5 years (**Figure 1**). The study recruited 114 patients, but 105 patients were included in the analysis (50 ventilated noninvasively and 55 ventilated invasively via tracheostomy) with equal gender distribution (**Table 1**, **Figure 2**). The study excluded nine patients for whom indication for the NIV initiation was established, but the ventilation had not been initiated due to lack of cooperation. The median age at the time of HMV initiation was 6.2 years (range: 0.3–18 years) with median age of 13 years in the NIV group and 18 months in the group ventilated invasively ($p < 0.01$). Although this difference is highly statistically significant, severe initial clinical presentation and rapid deterioration were met at an early age in most of the tracheotomized patients.

Patients were classified into four categories: NMDs, OSAS, syndrome of congenital central hypoventilation (CCHS), and primary respiratory diseases [11 patients with cystic fibrosis (CF) and three with severe forms of bronchopulmonary dysplasia]. NMDs have the largest prevalence (79/105 subjects or 75%) with spinal muscular dystrophy (SMA) and Duchenne muscular dystrophy (DMD) being the most frequent (**Figure 3**). The group referred as "other NMD" included patients with neurometabolic diseases and congenital myopathies. Although contributions of each group had not changed significantly since 2010 ($p = 0.13$), relative contribution of NMD increased from 62 to 75%.

HMV Strategy

The number of invasively and non-invasively ventilated patients was almost equal, as evident in **Figures 2**, **3**. Even though the number of invasively ventilated subjects surpassed the number of those non-invasively ventilated since 2012, analyses did not demonstrate statistically significant difference in the number between the groups ($p = 0.16$). The invasive ventilation protocol had been initiated significantly earlier than NIV ($p < 0.01$) as seen in **Table 1**. NIV was performed via nasobuccal masks in 22 patients (44%) and via nasal masks (including nasal pillows) in 18 cases (36%), while the rest of the participants received a combined ventilation with both types. The combination of

TABLE 1 | Demographic data.

	Non-invasive ventilation	Invasive ventilation	Total
Number of subjects	50	55	105
Sex (M/F)	28/22	27/28	55/50
Underlying disease			
NMD	28	51	79
Primary respiratory diseases	12	2	14
CCHS	3	2	5
OSAS	7	–	7
Age at initiation of HMV (median in years with range)	13 (0.75–18)	1.5 (0.3–17.9)	6.2 (0.3–18)
Duration of HMV (median in months)	42 (3–180)	36 (3–216)	38 (3–180)
Overnight ventilation	49	12	61
Ventilation 24 h a day	1	43	44
Died	10	15	25

NMD, neuromuscular disease; CF, cystic fibrosis; CCHS, congenital central hypoventilation syndrome; OSAS, obstructive sleep apnea syndrome; HMV, mechanical ventilation at home.

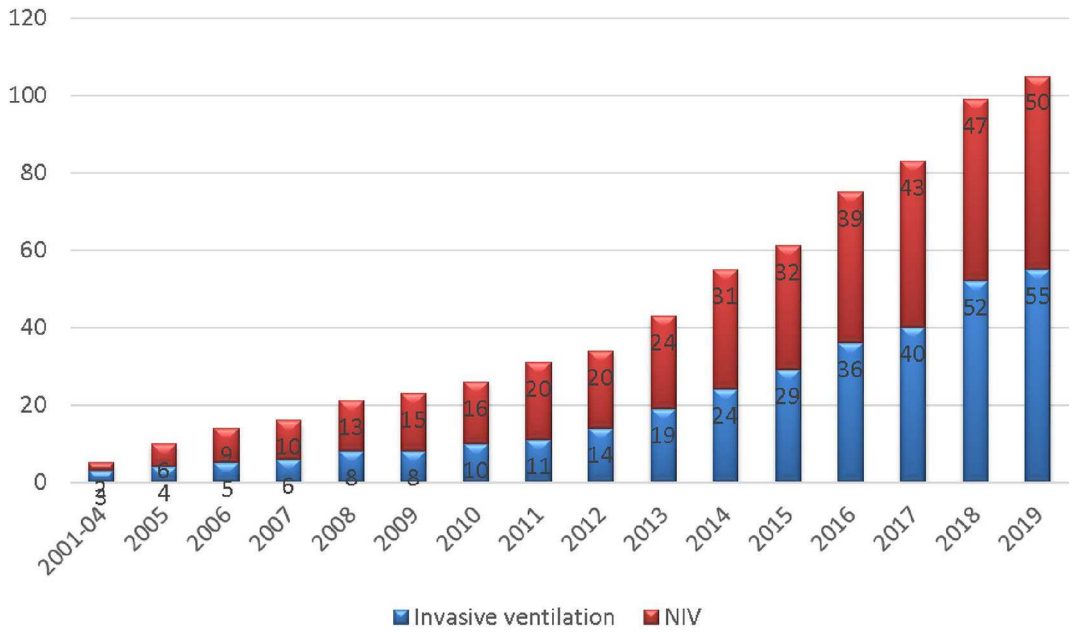

FIGURE 2 | Total number of patients.

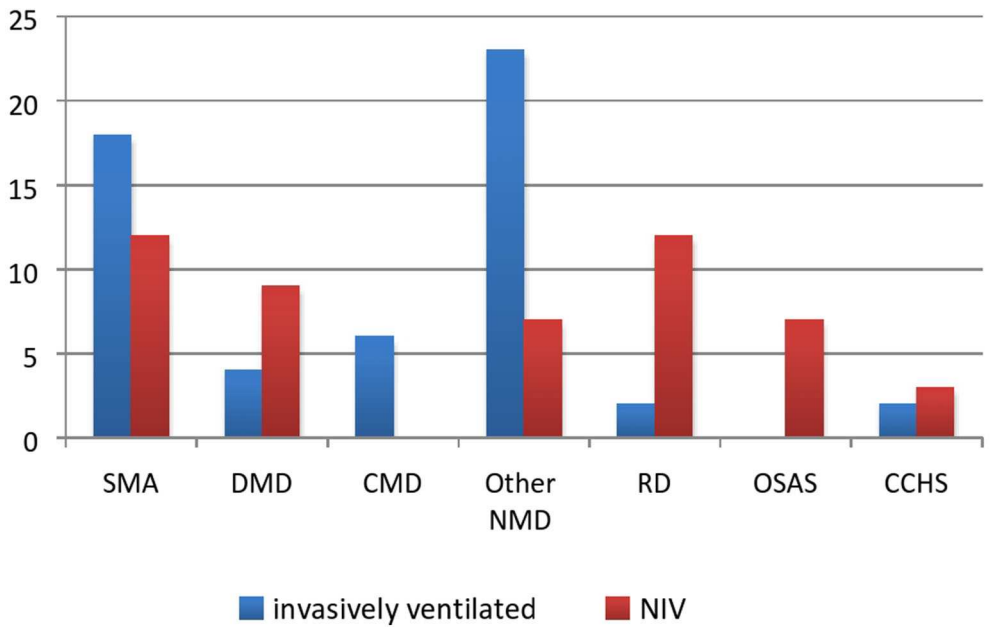

FIGURE 3 | HMV strategy in each group. SMA, spinal muscular dystrophy, DMD, Duchenne muscular dystrophy, CMD, congenital myotonic dystrophy; other NMD, other neuromuscular disease; PRD, primary respiratory disease; OSAS, obstructive sleep apnea syndrome; CCHS, congenital central hypoventilation syndrome.

different masks was allowed on patient's demand in order to improve both compliance and comfort, as well as to prevent facial deformities. Unfortunately, mouthpiece ventilation has not been available for our patients.

Patients with diurnal hypoventilation and rapid progression of respiratory failure accompanied by bulbar dysfunction were continuously ventilated via tracheostomy including those with SMA type 1 and congenital myotonic dystrophy, as well as a great proportion of patients with SMA types 2/3 (7/17–41%) and DMD (4/13–30%). Patients diagnosed with NMD and neurometabolic diseases who were admitted in the ICU in an acute respiratory deterioration requiring endotracheal

intubation would be eventually tracheotomized after the failure to wean.

Invasive ventilation in these subjects was in strong correlation to the lack of proper evaluation from the previous pulmonologist ($S = 6{,}049$, $p < 0.01$). Unfortunately, the lack of proper evaluation from the pulmonologist was the consequence of both non-attendance for arranged appointments and inadequate evaluation in regional hospitals.

NIV was performed in all others and was undertaken electively in most of the cases (44/50 or 88%). In addition, five patients initially started on NIV were eventually tracheotomized due to inadequate ventilation, while one patient with CCHS, primarily ventilated invasively, was decannulated and switched to NIV (14).

The average waiting time on equipment was counted from the day on which the decision for HMV was made up to the day when ventilation had started. It has changed significantly in recent years: 6 months of waiting until 2010 was shortened to just 1 month in 2019 ($W = 43.5$, $p < 0.01$).

The ventilator mode showed a strong correlation with the primary disease ($p < 0.01$). The pressure control mode (PC) was dominant in patients with NMDs who were invasively ventilated, while pressure support (PS) was mainly used in NIV patients with NMD and CF. Patients diagnosed with OSAS were supported by CPAP or BiPAP.

The average duration of HMV was 48 months (range 3–216 months); tracheotomized patients were ventilated longer than non-invasively ventilated ones (51 months in comparison to 45), but the difference was not statistically significant ($p = 0.95$). Comparisons among the groups revealed a significant difference in the duration of HMV between patients with OSAS and CF ($p = 0.03$), while differences between NMD and CF that were significant in 2012 were not subsequently significant ($p = 0.21$). The longest ventilated patient diagnosed with muscular dystrophy of unknown origin spent 18 years on invasive HMV, while the longest noninvasively ventilated patient diagnosed with the same primary disease has been ventilated for 15 years.

Description of Outcomes

The number of children who died while using HMV was 25 out of the 105 (24%); 10 of them were on NIV, while 15 had been receiving invasive HMV.

A vast majority of patients died in the hospital. Four patients with CF died due to a progression of primary disease while waiting for lung transplant. Six patients with DMD died due to heart failure, four patients with numerous comorbidities died after surgical interventions, one patient died due to erosive gastritis, and one patient died due to pulmonary hemorrhage. Pneumonia was the main cause of death in six cases. Three patients died at home after the mechanical failure of the medical equipment.

Twelve patients (11%) outgrew pediatric age and have been referred to adult pulmonologists. Adherence to HMV was satisfactory, only 7 out of 105 patients (6%) included in the study had not adhered regularly and decided to stop the ventilation. With the exception of five patients who no longer needed HMV following improvement, the remaining 56 children on HMV continued to visit our center. Mortality rates in centers in other developing countries alongside general study data are summarized in **Table 2**.

TABLE 2 | Summary of studies from developing countries.

	Louis et al. (6)	Nathan et al. (9)	Bertrand et al. (10)
Number of patients	55	70	35
Invasive/NIV	39/16	10/60	26/9
Underlying disease			
NMD	33 (60%)	7 (10%)	12 (34%)
Primary respiratory diseases	–	40 (57%)	17 (48%)
CCHS	5 (9%)	–	2 (6%)
Age at initiation of HMV (median in years)	3.5	0.9	1
Duration of HMV (median in months)	42.5	12	21
Overnight ventilation	18 (33%)*	38 (54%)	N/A
Ventilation 24 h a day	26 (47%)	32 (46%)	N/A
Died	21 (38%)	10 (14%)	6 (17%)

Information lacking for 11 patients.

NIV, non-invasive ventilation; NMD, neuromuscular disease; CCHS, congenital central hypoventilation syndrome; HMV, mechanical ventilation at home.

DISCUSSION

After introducing modern diagnostic techniques alongside new therapeutic approaches and better overall health care, the number of ventilator-supported patients in our center increased four-fold. It is believed that this trend will continue in the future. The rapidly growing population of ventilator-supported patients, availability of the equipment, and improved care resulted in both prolongation of life and improvement of its quality. A proactive attitude led to dramatically decreased hospital expenses and hospitalization rates, particularly in NMD patients.

From the inception of the HMV program at our center, the main problem was the waiting time between clinical decision and commencement of ventilation owing to the lack of availability of the equipment. The problem was partially resolved by donations of charity organizations and the improvement of the reimbursement policy. Ventilators licensed for 24-h ventilation have increasingly become available for a selected population of patients. Reimbursement for ventilators was possible only for children with SMA and muscular dystrophies. However, the significantly increased number of ventilated patients compelled medical system authorities to improve efficacy of administrative procedures for the equipment. That was also partially enabled and facilitated by the economic growth of the country, in the last decade. According to the World Bank report, gross domestic product per capita increased from $5,674 in 2010

to $7,223 in 2018 (15)[1] In addition, better organization in decision-making process, awareness, and support of local communities and charity donations from different sources finally resulted in substantially shortened waiting time for ventilator use.

Discharge planning for each patient started in the hospital and finalized when all prerequisites were accomplished. Primarily, the requirements were that the patient's clinical status had to be stable and necessary equipment obtained, working, and in use. Finally, caregivers had to express their capability and willingness of managing the patients at home in order for the patient to be discharged. Due to non-existence of home-care organization, home visits were not possible. A majority of the patient's needs were provided by either families or distributors of the equipment. While being hospitalized, caregivers (mostly parents) were fully trained to care for the patient at home. The training included medical procedures such as aspiration, tube feeding, cough assist techniques, basic ventilator settings and significance, and meaning of different alarms. After discharge, caregivers were informed about the possibility of contact with hospital team for any medical issue. This practice is comparable with the practices from other developing countries (9, 10).

However, a high proportion of invasively ventilated patients remain, despite all efforts to shift from invasive ventilation to NIV. In most centers across developed countries, a vast majority of patients had been ventilated noninvasively (5, 16–19), while the strategy of administrating HMV in less developed counties differs among centers (6, 9, 10). In our center, the two groups were almost even, with a slightly higher number of invasively ventilated subjects. There could be a few possible explanations for this situation.

The vast majority of tracheotomized patients were those with underlying NMDs initially admitted and intubated mostly due to respiratory infections with subsequent extubation failure. In our center, the decision about starting long-term respiratory support at home is the exclusive jurisdiction of pediatric pulmonologists. The primary goal was NIV, but in case of its failure, invasive ventilation would be initiated. A Eurovent study showed that only 24% of subjects with underlying NMD were tracheotomized (5). Most notably, all patients diagnosed with SMA type 1 and a significant proportion of subjects with SMA type 2 and DMD were invasively ventilated. While the approach of ventilation for SMA type 1 patients differs among centers, combining NIV during the night and mouthpiece ventilation during daytime had been widely recognized for respiratory support in SMA type 2 and DMD (20–24) patients. We consider timing as probably one of the main limitations; late commencement of ventilator support can be a key factor for acute respiratory deteriorations during respiratory infections leading to ICU admission and subsequent weaning failure. Nevertheless, in some patients with severe mental disability, resistant epilepsy, or bulbar insufficiency, invasive ventilation remains the best choice. Only a year after its initiation, a new oligonucleotide-based therapy (Nusinersen) for SMA patients became available in Serbia. Although useful in the very early stages of SMA, such an expensive medical therapy could be afforded only by patients in wealthier health systems, where all other prerequisites were fulfilled for efficient and safe HMV protocol administration. We are convinced that relatively inexpensive HMV equipment needs to be prioritized instead of therapies whose true benefits on respiratory outcome need to documented.

Advanced overall health care in the previous decade and initiation of the lung transplantation program since 2013 significantly improved the quality of life of the most severe patients diagnosed with CF. Initially, NIV was intended for CF patients as a bridge to transplant or as a palliative procedure, although NIV has been shown to unload respiratory muscles, improve alveolar ventilation during sleep and exercise, and facilitate the recovery of an acute exacerbation (25, 26). In recent years, we started NIV in CF patients with documented nocturnal hypoventilation, which had positive impact on preservation of respiratory function and diminished annual exacerbation rates.

There are several possible reasons for the relatively small number of OSAS patients, which is inconsistent with results of different national surveys from developed countries (18). Primarily, we speculate that the small proportion of patients with OSAS in our survey is probably caused by the inexistence of systematic national screening procedures for patients with SDB. Additionally, many patients had a combination of different contributing factors that resulted in SDB—obesity and adenotonsillar hypertrophy, in particular. Resolving one of these by adenotonsillectomy resulted in improvement of symptoms and better results of a sleep study. If one considers that CPAP/BiPAP equipment is not reimbursable, only patients with severe SDB after surgery will be started on NIV. An interesting example is the situation with patients with Prader–Willi syndrome (PWS). It is a rare disease with an estimated prevalence of 1 in 10,000 to 1 in 25,000 live births. In Serbia, annual birth rate is 50,000 newborns; thus, 2–5 new patients with PWS is expected every year. Diagnosis is mostly confirmed at infancy by genetic testing in several national tertiary pediatric hospitals. Until 2012, we had three adolescent PWS patients on BiPAP, but none in the last 7 years. In many of the PWS patients, growth hormone (GH) therapy leads to general clinical status improvement, including positive body composition changes and improvements in psychomotor development. A sleep study is recommended to assess complex patterns of SDB in each PWS patient prior to initiation of GH therapy. We can presume that a sleep study was not performed in every PWS patient, although these patients have complex patterns of SDB (27). This issue was discussed recently with other team members and hopefully will be resolved in the future.

Every 3–4 months, checkups were organized for each patient. These follow-up visits included measurements of overnight gas exchange, followed by arterial blood gases after awakening. Preset values, ventilator mode, and trigger sensitivity were carefully evaluated and eventually changed according to the results. The evaluation of patient's compliance, alarm history, and further analysis of delivered/obtained volume or pressure became possible in the last few years with technical improvements of the in-built software. A national program of palliative care in pediatrics was initiated a few years ago with the aim of

[1]https://www.worldbank.org.

sharing knowledge and experience to mobilize regional hospitals in Serbia for early diagnosis and further care and follow-up of children on HMV, in close cooperation with the national center (28).

At the end, few limitations of this study should be underlined. Firstly, a retrospective study design will lack some necessary information. In addition, it represented a relatively inhomogeneous group with a proportionately low number of patients with OSAS, because of the inexistence of systematic national screening for SDB. Finally, a small percentage of NMD patients were timely evaluated, which affects clinical practice and resulted in a high proportion of patients having been ventilated invasively.

CONCLUSION

In the last decade, our national HMV program has been conducted successfully, despite numerous obstacles during that period. Both availability and shortened waiting time for modern ventilator equipment accompanied by advanced overall health care are basics of substantial improvement. With our experience, in a relatively small developing country such as Serbia, one well-organized HMV center is adequate. A well-developed national network of regional hospitals that spreads knowledge and exchanges experiences with other pediatric pulmonologists is of great importance. In future, improvements could be directed to emphasize the importance of early diagnosis of SDB and nocturnal hypoventilation as an early sign of respiratory failure to avoid acute deterioration and potential subsequent invasive ventilation. We also hope that equipment for HMV will be available to all the affected children, regardless of primary cause of disease.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of The Institute for Health Protection of Mother and Child of Serbia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MB contributed in literature search, data collection and organization of database, study design, statistical analysis, manuscript preparation, and manuscript revision. PM contributed in statistical analysis, manuscript preparation, and manuscript revision. MR contributed in data collection and organization of database, study design, and manuscript revision. AS contributed in literature search, data collection and organization of database, study design, statistical analysis, manuscript preparation, and manuscript revision.

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