Children with neuromuscular disorder (NMD) usually have pulmonary involvement characterized by weakened respiratory muscles, insufficient coughing, and inability to clear airway secretions. When suffering from community-acquired pneumonia, these patients are more likely to develop acute respiratory failure (ARF). Therefore, recurrent pneumonias leading to acute on chronic respiratory failure accounts for a common cause of mortality in children with NMD. For many years, noninvasive ventilation (NIV) has been regarded as a life-prolonging tool and has been used as the preferred intervention for treating chronic hypoventilation in patients with advanced NMD. However, an increasing number of studies have proposed the utility of NIV as first-line management for acute on chronic respiratory failure in NMD patients. The benefits of NIV support in acute settings include avoiding invasive mechanical ventilation, shorter intensive care unit or hospital stays, facilitation of extubation, and improved overall survival. As the difficulty in clearing respiratory secretions is considered a significant risk factor attributing to NIV failure, combined coughing assistance of mechanical insufflator-exsufflator (MI-E) with NIV has been recommended the treatment of acute neuromuscular respiratory failure. Several recent studies have demonstrated the feasibility and effectiveness of combined NIV and MI-E in treating ARF of children with NMD in acute care settings. However, to date, only one randomized controlled study has investigated the efficacy of NIV in childhood ARF, but subjects with underlying NMD were excluded. It reflects the need for more studies to elaborate evidence-based practice, especially the combined NIV and MI-E use in children with acute neuromuscular respiratory failure. In this article, we will review the feasibility, effectiveness, predictors of outcome, and perspectives of novel applications of combined NIV and MI-E in the treatment of ARF in NMD children.

Keywords: noninvasive ventilation, neuromuscular disorder, acute respiratory failure, mechanically assisted coughing, risk factors
PATHOPHYSIOLOGY UNDERLYING ACUTE RESPIRATORY FAILURE IN CHILDREN WITH NEUROMUSCULAR DISORDER

Neuromuscular disease (NMD) is a heterogeneous group of diseases caused by various defects from multiple sources, including skeletal muscle, motor neurons, peripheral nerves, and neuromuscular junctions (1-4). Most primary NMD is associated with an inherited gene defect and usually onset in childhood with progressive degeneration. Due to weakened either one or all of the main respiratory muscle groups and impaired coughing ability, the respiratory dysfunction represents not only a critical health issue but a frequent unmet medical need of NMD patients (2, 5, 6).

Children with NMD may have progressively developed chronic respiratory failure in the process of disease course. However, episodic attacks of acute respiratory failure (ARF) may further aggravate the already existed respiratory compromises (7). Factors posing a risk of ARF in children with NMD are usually multifactorial and occur simultaneously (8-11). Table 1 summarizes the risk levels of various NMD potentially affected by the acute respiratory compromise. According to the timing of ARF occurrence, NMD can also be classified into two main categories: (1) early-onset (may as early as in neonatal period) with rapidly progressive NMD with acute episodes of respiratory failure; (2) late-onset and slowly progressive NMD with acute exacerbations of chronic respiratory failure (12, 14).

As shown in Figure 1, the pathophysiological mechanism of respiratory muscle groups involved in NMD patients can be summarized into three main components and several predisposing factors (6, 7, 9, 13, 14). First, the weakness of bulbar muscles impedes the protection against the risk of aspiration

| Primarily affected age group | Risk level of ARF occurrence | Affected NMD |
|-----------------------------|-----------------------------|--------------|
| At birth or within the first year of life | Usually inevitable if untreated | Spinal muscular atrophy (SMA) type 1 (if untreated)*  
Spinal muscular atrophy with respiratory distress (SMARD)  
Congenital myotonic dystrophy (type 1)  
Infantile Pompe disease (if untreated)*  
Some congenital myopathies (e.g., neonatal form of nemaline myopathy, minicore myopathy, and X-linked myotubular myopathy)  
Some congenital muscular dystrophies (CMD) (e.g., Walker-Warburg syndrome and Muscle-eye-brain disease)  
Some mitochondrial diseases  
Some congenital myasthenic syndromes |
| Infant-to-adult life | Very high risk | Some limb-girdle muscular dystrophy (LGMD), especially with sarcoglycanopathies (LGMD types 2C, 2D, 2E, 2F) and LGMD type 2I  
Some CMD, especially merosin negative types 1A, 1B, 1C  
Some myofibrillar myopathies (e.g., hereditary myopathy with early respiratory failure)  
Early-onset infantile facioscapulohumeral muscular dystrophy (FSHD)  
Early-onset Charcot-Marie-Tooth disease (CMTD) especially with GDAP1 mutation  
Some congenital myopathies (e.g., severe recessive type of central core myopathy) |
| Infant-to-adult life | High risk | Duchenne muscular dystrophy (DMD), usually after second decade  
SMA type 2  
Myotonic dystrophy type 1 (DM1)  
Late-onset Pompe disease (LOPD)  
Some CMD (e.g., Ullrich type, and Fukuyama congenital muscular dystrophy)  
Some LGMD (e.g., calpainopathy)  
Some congenital myopathies (e.g., centronuclear myopathy)  
Bethlem myopathy  
Congenital myasthenic syndromes  
Some mitochondrial myopathies (e.g., A3243G mutation in the tRNALeu gene) |
| Intermediate risk | Becker muscular dystrophy (BMD)  
SMA type 3  
Inflammatory myopathies (e.g., polymyositis, dermatomyositis)  
Classical type of FSHD  
Some types of Charcot-Marie-Tooth disease (e.g., CMTD type 1B and 4)  
Some congenital myopathies  
Some mitochondrial myopathies  
Guillain-Barré syndrome (GBS)  
Myasthenia gravis (MG) |
| Low risk | Oculopharyngeal muscular dystrophy (OPMD)  
Other types of CMTD  
Chronic inflammatory demyelinating polyneuropathy (CIDP) |

*Novel therapies are currently available (e.g., enzyme replacement, antisense nucleotide, and gene therapy) to be delivered in the neonatal period.

Data of this table are modified and summarized from references: (11-13).
of the food or airway secretions, which may lead to frequent
atelectasis and pneumonia (14). Additionally, weakness of bulbar
muscles and tongue, and paralysis of vocal cords may cause
mechanical obstruction of the upper airway, particularly in
the supine position, and increase the likelihood of aspiration
(9, 14). Second, weakness of the inspiratory muscles leads to
reduced lung expansion and impaired coughing ability, which
may lead to a ventilation/perfusion mismatch and consequent
hypoxemia. Compensatory tachypnea due to small tidal volumes
may further increase the mechanical load on already weakened
respiratory muscles (6, 7, 13). Third, the weakness of expiratory
muscles leads to ineffective coughing and encumbrance of airway
secretion, which consequently increases breathing load (14).

On the other hand, other systemic involvements associated
with NMD may further aggravate the impairment of lung
function, which precipitate the occurrence of ARF (5, 6, 14,
15). In the advanced stage of NMD, progressive scoliosis is
common and usually causes reduced chest wall compliance and
unequal lung expansion. Patients with certain types of NMD,
such as Duchenne muscular dystrophy and Emery-Dreifuss
muscular dystrophy, frequently have cardiac involvement that
may further worsen the respiratory function (e.g., pulmonary
edema related to congestive heart failure) (11, 12). ARF
may also occur in the perioperative period of some major
surgeries, for example, correction of scoliosis or insertion of
percutaneous gastrostomy. Such ARF episodes usually happen
after extubation and are associated with bulbar dysfunction,
postoperative pain, use of pain medications, or atelectasis caused
by mucus plugging (16, 17). Malnutrition and dehydration
developing during an acute illness should be aggressively
intervened, as unmet caloric and metabolic needs may further
aggravate ARF. Thus, each of these comorbidities necessitates
multidisciplinary interventions and meticulous monitoring (5,
18–23).

In most cases, the occurrence of ARF in children with NMD is
usually initiated by an upper respiratory tract infection, followed
by complications of congested airway secretions, mucus plugs,
and atelectasis (9, 24, 25). In addition, increased nasal airflow
resistance with nasal congestion in the setting of pre-existing
upper airway obstruction from bulbar dysfunction also increases
respiratory muscle load in the absence of bronchial secretions.
Due to community pneumonia, the decreased lung compliance
and the increased workload of already weak muscles may further
contribute to the onset of ARF (6). Among children with
NMD, ARF is the main cause of unscheduled admissions and
prolonged stay in the pediatric intensive care unit (ICU) (11, 26).
Moreover, complications known to be associated with prolonged
ICU stay and conventional invasive mechanical ventilator (IMV)
may also contribute to high ICU mortality (27, 28). As a
consequence, acute-on-chronic respiratory failure represents the
most common cause of morbidity and mortality in children with
NMD (9, 29).
NONINVASIVE VENTILATION IN CHILDHOOD ACUTE NEUROMUSCULAR RESPIRATORY FAILURE

In the past few decades, noninvasive ventilation (NIV) has been regarded as a life-prolonging tool for managing chronic respiratory failure in patients with NMD (6, 11, 21, 30). On the other hand, recent studies and guidelines have also proposed the role of NIV as a first-line intervention for ARF in NMD patients to avoid endotracheal intubation and the use of invasive mechanical ventilation (IMV) (11, 31, 32). Support for alternative use of NIV is based on concerns about the many complications of IMV use in patients with NMD. These include laryngeal edema, subglottic stenosis, barotrauma, and ventilator-associated pneumonia, leading to subsequent tracheotomy and poor quality of life (17, 33–35). Besides, long-term dependence on IMV and prolonged ICU stay are associated with nosocomial infections, aspiration, atelectasis, thromboembolic events, contractures, and bedsores, all of which can lead to high mortality in NMD patients (8). In this regard, emerging evidence supports the alternative NIV administration to manage ARF in patients with NMD (36–38). Indeed, several studies have indicated several potential benefits of NIV in treating ARF of NMD patients, including shortening the ICU and hospital stay, facilitating extubation, and improving the overall survival (16, 39–42).

ROLE OF AGGRESSIVE SECRETION MANAGEMENT IN MANAGING ARF OF NMD CHILDREN

Mucociliary clearance is generally not affected by NMD, except for damage to the ciliary epithelium due to repeat aspiration or acute chest infection (43). Aggressive secretion clearance is crucial for children with NMD to avoid progression to severe respiratory compromises during respiratory infections (44, 45). Also, excessive secretion has been regarded as a major risk factor causing NIV failure in treating ARF of NMD patients (6, 46, 47). Therefore, facilitating secretion clearance and normalizing gas exchange by augmenting cough ability is the mainstay to treat ARF in children with NMD (48).

Although NMD patients rarely achieve sufficient chest and abdomen pressure due to the weakness of the intercostal and abdominal muscles, the coughing can be augmented manually or mechanically. Among various coughing-assist techniques, the mechanical insufflator-exsufflator (MI-E) represents the most powerful tool that can promote the most effective peak flow to expel mucus plugging and resolve atelectasis (7, 49, 50). MI-E can deliver a brief positive inspiratory pressure through a mask, mouthpiece, tracheostomy, or endotracheal tube to fully expand the chest, allowing air to enter the distal end of the mucus plugging, and then applying negative pressure, resulting in expiratory “cough” flow to remove airway secretions (45). A previous study showed that MI-E is superior to manual cough assistance in increasing cough flow in healthy subjects as well as in patients with amyotrophic lateral sclerosis (ALS), regardless of bulbar weakness (51). The additional use of MI-E helps to resolve excessive secretions and eliminate the risk of NIV failure in treating ARF of NMD patients. Therefore, recent evidence suggests that combining NIV and MI-E can be used as the first-line treatment for ARF in children with NMD (14, 44, 45, 47, 50). Our experiences also show that it can effectively treat ARF even for the most severe types of NMD (Figure 2).

EFFECTIVENESS OF NIV IN POST-EXTUBATION SUPPORT FOR CHILDREN WITH NMD

After recovering from an acute illness or surgery requiring sedation, a considerable number of NMD patients may not pass the IMV-dependent weaning tests, resulting in a high failure rate.
of extubation (26–28). Post-extubation ARF in NMD patients shares several pathomechanism features with episodic ARF, such as weak respiration drive, airway mucus-plugging due to difficulty in expectorating secretion, mostly categorized as type 2 (hypercapnic) ARF (28). The advent of active NIV support reduces the need for extensive weaning trials before extubation, which requires prolonged pressure support and spontaneous breathing. Some studies have validated that prompt NIV and MI-E use after extubation can significantly eliminate the risk of reintubation in NMD patients (40, 52, 53). There is a general agreement that, if not contraindicated (e.g., uncontrolled airway secretions or severe bulbar dysfunction), patients with chronic NMD should be extubated directly to NIV combined with MI-E (28, 54). The effectiveness of this NIV support is significant in preventing reintubation in young children with NMD (Figure 3).

**FIGURE 3 |** Demonstration of chest X-ray in a toddler with congenital myopathy who immediately received NIV and MI-E for post-extubation respiratory support. (A) Previously failed extubation in another hospital was related to frequent right lung atelectasis and mucus plugging developing soon after extubation. (B) In our hospital, appropriate expansion of both lungs were noted before extubation. (C) Day 2 post-extubation showed mild right lung infiltration without atelectasis. (D) Discharge from PICU on day 7 post-extubation showed re-expansion of both lungs.

**REVIEW OF CLINICAL STUDIES ON NIV FOR THE TREATMENT OF ACUTE-ON-CHRONIC NEUROMUSCULAR RESPIRATORY FAILURE**

There are relatively few prospective studies on the management of NMD patients with ARF, which may be because most chronic NMDs are rare diseases, making it difficult to recruit patients. As shown in Table 2, evidence that NIV can help avoid intubation of patients with chronic NMD during the ARF episodes comes from 11 non-randomized observational studies of a total of 178 subjects (age range 2 months to 69 years), of which most subjects are known to be under 25 years (36, 37, 39–42, 52, 53, 56, 57). However, in most studies, there are few descriptions of methods to manage airway secretions, and its role in contributing to the success of NIV in treating ARF is not well defined (45). Even though an increasing number of studies have recognized the benefit of combined NIV and MI-E use in the ARF management and facilitation of extubation in adult NMD patients (37, 40, 54), similar studies on the pediatric NMD populations are scarce. In heterogeneous pediatric populations, several risk factors for predicting the failure of NIV treatment fo ARF have been reported (11, 32, 44), but it is still unclear whether similar factors exist in a specific pediatric NMD population.

However, only one randomized controlled study has investigated the efficacy of NIV in treating children with ARF but has excluded children with underlying NMD (31). Two recent studies reported by the same team described the protocol and effectiveness of a combination of NIV with MI-E in treating ARF of children with chronic NMD (52, 57). The pilot study of children encompassing various NMDs has demonstrated the feasibility of this combined noninvasive approach. The following research on a larger cohort of NMD patients further verified its safety and effectiveness. Overall, combining the data of these two studies on 71 NMD patients shows that timely implementation of NIV and MI-E can avoid intubation or reintubation in 75–86% of ARF events, of which 80% are pediatric cases. The PICU and hospital stay of children successfully rescued through NIV/MI-E is shorter than that of children who received intubation. Besides, several predictors of NIV failure were identified, including physical parameters (changes in respiratory rate) and laboratory variables (changes in PaCO₂ and pH value of arterial blood gas).

**COMBINED NIV AND MI-E IN ARF TREATMENT OF NMD CHILDREN**

The interface connects the ventilator tubing to the patient to deliver pressurized gas to the airway during NIV administration. It may take several attempts to find a suitable interface, but this is the key to successfully treating ARF in NMD children with NIV while minimizing air leakage, maximizing patient comfort, and synchronizing with the ventilator (44, 58, 59). However, although interface tolerance is a pivotal factor associated with NIV success, comparative data on the interface of infants and young children is scarce (60).

A transparent interface is highly recommended to ensure correct positioning and enhance patient monitoring (59). The medical team should be well trained to select the most suitable interface individualized for each critically ill child (61). As proof of principle, the smallest interface with the least air leakage should be selected to minimize the dead space. For infants,
| References          | Study Design                      | Number of NMD patients (age) | NMD diagnosis (n) | ARF types* (n, %) | NIV/interface/secretion clearance | Success rate and main findings                                                                 | Predictor of NIV failure | NIV Complications (n) | Limit                          |
|---------------------|----------------------------------|-----------------------------|-------------------|------------------|----------------------------------|-----------------------------------------------------------------------------------------------|--------------------------|------------------------|--------------------------------|
| Padman et al. (39)  | Monocenter retrospective study   | 11 patients; (range: 4-21 y)| DMD (?), SMA (2), SCI (1), nonspecific myopathy (1) | Type 2 (11, 100%) | BLPAP via nasal mask             | • NIV success rate (no intubation): 91% • Improved RFI, PaCO₂, serum bicarbonate, and length of hospitalization after NIV use | None identified            | No major complications  | Hypoxic ARF and significant difficulty handling secretions |
| Birnkrant et al. (55) | Monocenter retrospective study  | 8 patients (range 1-18 y)   | DMD(5), SMA(3)    | Undefined ARF, including 3 post-extubation ARF | BLPAP via nasal interface | Allowed weaning from an invasive airway: 100% effective in avoiding ETI or facilitating extubation | None identified           | NA                     | Non described           |
| Niranjan and Bach (40) | Monocenter retrospective study | 10 patients (median: 17 y; range: 13-21 y) vs. 7 historical controls | DMD (8), SMA (1), SCI (1) | Type 2 (10, 100%), including 6 post-extubation ARF | BLPAP via mouthpiece or nasal interface + MI-E | • NIV success rate (no intubation): 100% • Shorter hospital stay in NIV group than historical control | None identified           | NA                     | Non described           |
| Bach et al. (56)    | Monocenter retrospective study   | 11 children with 28 ARF episodes (median: 6 m; range 2-11 m) | SMA type 1 (11)  | Post-extubation ARF (28, 100%) | BLPAP via nasal interface + MI-E for post-extubation support | • NIV success rate (no intubation): 82% • NIV can facilitate extubation for type 1 SMA children even with severe bulbar muscle weakness | None identified           | NA                     | Non described           |
| Vianello et al. (36) | Monocenter prospective case-control study | 14 patients (median: 24 y; range: 10-69 y) vs. 14 historical controls | DMD (7), ALS (4), CMD(1), HMSN (1), CM(1) | Type 2 (14, 100%) | E = BLPAP via nasal interface + cricothyroid-mini-tracheostomy; C = IMV via ETI | • NIV success rate (no intubation): 71% (14% mortality rate) vs. 21% of controls (57% mortality rate) • Lower mortality and complications, and shorter ICU stay of NIV group than controls • NIV combined with cricothyroid-mini-tracheostomy for secretion clearance was well tolerated without significant complications | None identified           | No major complications  | Severe bulbar involvement |
| Vianello et al. (37) | Monocenter prospective case-control study | 11 patients (median: 31 y; range: 16-64 y) vs. 16 historical controls | DMD (4), SMA (3), ALS (2), LGMD(1), FSHD (1) | Type 2 (11, 100%) | E = BLPAP via nasal interface + MI-E+CPT; C = BLPAP+CPT | • NIV success rate (no intubation): 82 vs. 37% of controls • No serious side effects and well-tolerated in all subjects with MI-E use | None identified           | Gastric distension (1), epistaxis (1) |
| Servera et al. (41) | Monocenter prospective cohort study | 17 patients (48.7±20.9 y) | ALS (11), DMD (4), transverse myelitis (1), nonspecific myopathy (1) | Type 2 ARF (17, 100%) | BLPAP via nasal/oronasal interfaces + MI-E | • NIV success rate (no intubation): 79.2% • Severe bulbar involvement limited NIV effectiveness | Bulbar dysfunction         | NA                     | Severe bulbar involvement NIV/MI-E performed in non-ICU settings |

(Continued)
| References        | Study Design                      | Number of NMD patients (age) | NMD diagnosis (n)                                                                 | ARF types* (n, %)                                                                 | NIV/interface/secretion clearance | Success rate and main findings                                                                 | Predictor of NIV failure | NIV Complications (n) | Limit                                                                 |
|------------------|----------------------------------|-----------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------|------------------------|----------------------|-----------------------------------------------------------------------|
| Piastra et al.   | Monocenter prospective observational cohort study | 10 children (4.1 ± 4.5 y; range 3 m-12 y) | SMA type 1(2), CMD-Ulrich (1), CM-nemaline CM (1), MG (2), mitochondrial myopathy (1), spinal cord hamartomatosis (1), nonspecific myopathies (2) | Type 2 (5, 50%); Type 1 (2, 20%); mixed/undefined (3, 30%) | BLPAP via facial mask or helmet+ CPT | • NIV success rate (no intubation): 80%  
• Hypercarbic ARF resolved within 6 h of NIV use  
• Oxygenation markers improved rapidly after NIV introduction | Airway obstruction | No major complications | Copious tracheal secretion needing frequent suction |
| Dohna-Schwake et al. | Monocenter retrospective study | 15 children (median: 6 y) | SMA (6), DMD (3), Pompe disease (2), CMD (2), myopathy (1), myotonic dystrophy (1) | Undefined ARF, including 2 post-extubation ARF | CPAP via mask | • NIV success rate (no intubation): 87%  
• Improved HR, RR, blood pH, PaCO₂, and SaO₂ after 1-2 h of NIV use in the success group | Low pH at 1-2 h after NIV | midface skin ulcers and gastric distension | 3 patients requested “do-not-intubate-status” |
| Chen et al.      | Monocenter prospective observational cohort study | 15 children with 16 ARF episodes (mean: 8.1 y; range 3 m- 18 y) | SMA (6), DMD (2), CM (2), MM (2), HMSN (2), LGMD 2i (1) | Type 2 (15, 94%) including 1 post-extubation ARF; Type 1 (1, 6%) | BLPAP via nasal/oronasal or facial mask + MI-E | • NIV success rate (no intubation): 75%  
• Improved blood pH, and PaCO₂ after 12 h of NIV use in the success group | Fewer decrement of RR after 3 h of NIV use | No major complications | |
| Chen et al.      | Monocenter prospective observational cohort study | 56 NMD patients (44 children) with 62 ARF episodes; median: 13 y; range: 2 m-39 y | SMA (32), DMD (14), CM (6), CMD (4), MM (4), HMSN (1), SMARD (1) | Type 2 ARF (53, 85%) including 23 post-extubation failure; Type 1 ARF (9, 15%) | BLPAP via nasal/oronasal or facial mask + MI-E | • NIV success rate (no intubation): 86%  
• Improved HR, RR, blood pH, and PaCO₂ after 4 h of NIV use in the success group  
• Shorter PICU and hospital stay of success group | RR decreased at 4 h; pH increased, and PaCO₂ decreased at 4-8 h after NIV | No major complications | Initial checking blood gases at a later point of 4-8 h after NIV |

*Type 1 ARF, Hypoxemic ARF; Type 2 ARF, hypercapnic ARF; NMD, neuromuscular disorders; NIV, non-invasive ventilation; ARF, acute respiratory failure; BLPAP, bi-level positive airway pressure; MI-E, Mechanical insufflator-exsufflator; E, experiment; C, control; CPT, chest physical treatments; DMD, Duchenne muscular dystrophy; SMA, spinal muscular atrophy; SCI, spinal cord injury, HMSN, hereditary motor and sensory neuropathy; CMD, congenital Muscular Dystrophy; CM, congenital Myopathy; MG, myasthenia gravis; MM, mitochondrial myopathy; SMARD, spinal muscular atrophy with respiratory distress; LGMD 2i, limb-girdle muscular dystrophy type 2i; NA, Not available.

CPAP, Continuous positive airway pressure.
nasal interface (nasal cannula, nasal prong, or nasal mask) is recommended the interface of first choice (6, 44). Otherwise, choosing the right interface for older children is usually based on available materials and training of an experienced medical team, not on scientific data. Generally, in older children and young adults with ARF, full oronasal face masks are preferable to nasal interfaces because of better tolerance and a better sealing with less air leak (60, 62). Although some studies have shown that the feasibility and effectiveness of helmets in infants and young children, the experience of using helmets as interfaces in children is even rarer (62). It should be kept in mind that there is no single interface suitable for all situations, and the use of these interfaces in NMD children, especially in the critical care setting, requires better evidence support (59).

Recommendations for the initial setting of NIV are mainly based on clinical experience and expert consensus as there are no consistent data on optimal settings. If not contraindicated as the list aforementioned, the initial settings chosen should be disease and device-specific. Importantly, the information regarding the potential contraindications or complications related to NIV administration in the NMD patient population should be addressed (6, 11). Generally, the administration of NIV support should be set low initially to allow patient acclimation and then increase according to the physiologic needs and patient tolerance. According to our protocol specialized for NMD children, bilevel positive airway pressure (BLPAP) with an adequate interface is always effective in rescuing ARF (52, 57). Especially during an acute chest infection, NIV should be used more intensively for these patients. Under adequate approaches of secretion clearance, supplemental oxygen may be added to NIV to maintain appropriate oxygenation. However, if the patient becomes almost whole-day dependent on NIV during an acute event, consider alternating masks to prevent pressure sores and alternate day and night between two ventilators of the same model so as not to run a ventilator continuously for days. The MI-E can be applied either in combination with NIV through a full-face mask or solitarily used in intubated patients via the endotracheal or tracheostomy tube with the cuff inflated. If applicable, supplementary manual augmentation of cough may be applied intermittently, followed by MI-E use.

In addition to noninvasive airway approaches, all other sensible standard measures can be taken during ARF episodes. These approaches include adapting a low threshold to deliver broad-spectrum antibiotics, adequate hydration, and attention to nutritional support. Humidification of the ventilator is often beneficial in reducing sputum viscosity and mobilizing secretions. Therapies of nebulized bronchodilator or systemic steroid may be considered if evidence of asthma or asthmatic bronchitis (10, 60).

From the perspective of chronic respiratory care, proactive use of NIV, and cough assistant MI-E in NMD children has been shown to reduce the rate of hospitalization and ICU admission (63–65). The familiarity of NMD patients with NIV use can help the effectiveness of NIV in the treatment of ARF (60). Several studies have shown that prior training of NIV and MI-E at home can contribute to a higher success rate in acute care settings (14, 52, 66). In this regard, the proactive use of NIV and MI-E in the routine respiratory care of children with chronic NMD may also be beneficial (65).

Besides MI-E, high-frequency chest wall oscillation (HFCWO) has recently been proposed as a potential intervention used to facilitate secretion clearance in NMD patients. HFCWO delivers pressure to the chest wall accompanied by high-frequency vibration, which shows to move secretions from peripheral airways toward more central airways (67). However, the safety and effectiveness of HFCWO have not been well studied in managing ARF of NMD children, and its benefit in acute care settings is unclear (68). There is still a lack of data on the safety and effectiveness of NMD infants and young children known to be more susceptible to consistent and high frequent oscillation waves. Further research on HFCWO in NMD children is needed.

CONTRAINDICATIONS AND COMPLICATIONS OF NIV AND MI-E

The patient selection remains the most critical factor for the success of NIV in treating ARF. The contraindications to the NIV use include hemodynamic instability, severely decreased consciousness level, severe bulbar dysfunction (i.e., absence of gag reflex, or vocal cord paralysis), un-drained pneumothorax, facial deformity or injuries, recent surgery of facial, upper airway, or upper gastrointestinal tract, intolerance to NIV interface, multi-organ failure, life-threatening hypoxemia (PaO₂ < 60 mmHg with FiO₂ > 0.6), and lack of familiarity of health-care provider with NIV operation (6, 14, 62, 69, 70).

In general, NIV is a safe approach in managing ARF of infants and children with NMD, and the adverse effects described are minor (71). However, similar to any ventilation therapy, there are some adverse reactions and severe complications worthy of understanding. Reducing complications of NIV and MI-E largely depends on the well-trained and experienced staff of a multidisciplinary care team (21, 44, 62, 72). Gastric distension may occasionally occur, which can be ameliorated by nasogastric tube insertion and keeping adequate enteral feeding. Barotrauma may occur, but the risk is extremely low during NIV and much lower than during mechanical ventilation (73). For patients with hypovolemia, NIV should be used with caution, because NIV can cause an additional increase in intrathoracic pressure, which may result in a decrease in venous return (preload) and further deteriorate cardiac output (74).

Agitation may develop, especially during the initial interface placement on a child, but it is not necessary to discontinue NIV for this reason. Pharmacological sedation may be required, especially for children with NMD who receive NIV for the first time (75, 76). Choosing a more comfortable interface and fine-tuning NIV settings can reduce the need for sedatives (62). Other related complications include skin lesions, discomfort, claustrophobia, nasal mucosa trauma, and conjunctivitis, which may be prevented by a sophisticated selection of appropriate interface, alternating interface intermittently, and humidification of the ventilator (59, 60).
CONCLUSIONS

The care of chronically progressive NMD has evolved significantly in the last decade, and many NMD children are now achieving prolonged survival through the advances in novel treatments (e.g., gene and molecular therapies) as well as respiratory care. However, there is still no consensus on the timing and limitations of NIV use in the treatment of ARF in children with NMD. Therefore, the administration protocol must be integrated with individualized clinical judgment. NMD usually includes various diseases of different severity, and the pathomechanism of ARF may vary with the type of NMD. Thus, it is unclear whether certain types of NMD may be more sensitive to NIV treatment for ARF. The variety and complexity of specific problems presented by different NMD necessitate separate remarks on the early recognition and adequate management of ARF in children with NMD. More future researches designed specifically for the pediatric NMD population are still needed, and several issues remain to be clarified.

AUTHOR CONTRIBUTIONS

T-HC and J-HH contributed to conception and design, acquisition of data, revising the manuscript critically for relevant intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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REFERENCES

1. Aslan GK, Gurses HN, Isever H, Kiyan E. Effects of respiratory muscle training on pulmonary functions in patients with slowly progressive neuromuscular disease: a randomized controlled trial. Clin Rehabil. (2014) 28:573–81. doi: 10.1177/0269215513512215
2. Howard RS. Respiratory failure because of neuromuscular disease. Curr Opin Neurol. (2016) 29:592–601. doi: 10.1097/WCO.0000000000000363
3. Boentert M, Wenninger S, Sansome VA. Respiratory involvement in neuromuscular disorders. Curr Opin Neurol. (2017) 30:529–37. doi: 10.1097/WCO.0000000000000470
4. Hocker S. Primary acute neuromuscular respiratory failure. Neurol Clin. (2017) 35:707–21. doi: 10.1016/j.ncl.2017.06.007
5. Yuan N. Neuromuscular disease and the pulmonologist. Curr Opin Pediatr. (2012) 24:336–43. doi: 10.1097/MOP.0b013e3283531b00
6. Panitch HB. Respiratory implications of pediatric neuromuscular disease. Respir Care. (2017) 62:426–48. doi: 10.4187/respcare.05250
7. Benditt JQ, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease. Am J Respir Crit Care Med. (2013) 187:1046–55. doi: 10.1164/rccm.201210-1840CI
8. Mehta S. Neuromuscular disease causing acute respiratory failure. Respir Care. (2006) 51:1016–21; discussion 21–3.
9. Panitch HB. The pathophysiology of respiratory impairment in pediatric neuromuscular diseases. Pediatrics. (2009) 123 Suppl 4:S254–5. doi: 10.1542/peds.2008-2952K
10. Vouglaris A, Antoniadou M, Agrafiotis M, Steiropoulos P. Respiratory involvement in patients with neuromuscular diseases: a Narrative review. Pulm Med. (2019) 2019:2734054. doi: 10.1155/2019/2734054
11. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British thoracic society guideline for respiratory management of childhood progressive neuromuscular disease. Arch Dis Child. (2015) 100:172–7. doi: 10.1136/archdischild-2014-308206
12. Shahrizaila N, Kinnear WJ, Wills AJ. Respiratory involvement in inherited primary muscle conditions. J Neurol Neurosurg Psychiatry. (2006) 77:1108–15. doi: 10.1136/jnnp.2005.078881
13. Rezania K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. Neurol Clin. (2012) 30:161–85, viii. doi: 10.1016/j.ncl.2011.09.010
14. Racca F, Del Sorbo L, Mongini T, Vianello A, Ranieri VM. Respiratory management of acute respiratory failure in neuromuscular diseases. Minerva Anestesiol. (2010) 76:51–62.
15. Hill NS. Neuromuscular disease in respiratory and critical care medicine. Respir Care. (2006) 51:1065–71.
16. Khirani S, Bersanini C, Aubertin G, Bachy M, Vialle R, Fauroux B. Noninvasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. Eur Spine J. (2014) 23 Suppl 4:S406–11. doi: 10.1007/s00586-014-3335-6
17. Bach JR, Goncalves MR, Hon A, Ishikawa Y, De Vito E, Prado F, et al. Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. Am J Phys Med Rehabil. (2013) 92:267–77. doi: 10.1097/PHM.0b013e31826ecd1
18. Wang CH, Bonnemann CG, Rutkowski A, Sejersen T, Bellini J, Battista V, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol. (2010) 25:1559–81. doi: 10.1177/0883735810381924
19. Wang CH, Dowling JJ, North K, Schroth MK, Sejersen T, Shapiro F, et al. Consensus statement on standard of care for congenital myopathies. J Child Neurol. (2012) 27:363–82. doi: 10.1177/0883735812436605
20. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. (2007) 22:1027–49. doi: 10.1097/JCN.0b013e3180305788
21. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. (2018) 28:197–207. doi: 10.1016/j.ncl.2017.11.004
22. Schroth MK. Special considerations in the respiratory management of spinal muscular atrophy. Pediatrics. (2009) 123 Suppl 4:S245–9. doi: 10.1542/peds.2008-2952K
23. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. (2010) 9:177–89. doi: 10.1016/S1474-4422(09)70272-8
24. Poponick JM, Jacobs I, Supinski G, DiMarco AF. Effect of upper respiratory tract infection in patients with neuromuscular disease. Am J Respir Crit Care Med. (1997) 156(2 Pt 1):659–64. doi: 10.1164/ajrccm.156.2.9611029
25. Katz SL, Gaboury I, Keilty K, Banwell B, Vajsar J, Anderson P, et al. Nocturnal hypoventilation: predictors and outcomes in childhood progressive neuromuscular disease. Arch Dis Child. (2010) 95:998–1003. doi: 10.1136/adc.2010.182709
26. Yates K, Festa M, Gillis J, Waters K, North K. Outcome of children with neuromuscular disease admitted to paediatric intensive care. Arch Dis Child. (2004) 89:170–5. doi: 10.1136/adc.2002.019562
27. Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. Arch Neurol. (2010) 67:1089–94. doi: 10.1001/archneur.2010.207
28. Vianello A, Arcaro G, Braccioni F, Gallan F, Marchi MR, Chizio S, et al. Prevention of extubation failure in high-risk patients with neuromuscular disease. J Crit Care. (2011) 26:517–24. doi: 10.1016/j.jcrc.2011.12.008
29. Katz S, Selvadurai H, Keilty K, Mitchell M, MacLusky I. Outcome of noninvasive positive pressure ventilation in paediatric neuromuscular disease. Arch Dis Child. (2004) 89:121–4. doi: 10.1136/adc.2002.018655
30. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* (2018) 28:103–15. doi: 10.1016/j.nmd.2017.11.005

31. Yanex Lj, Yunge M, Eminfork M, Lapadula M, Alcantara A, Fernandez C, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med.* (2008) 9:484–9. doi: 10.1097/PCC.0b013e318184989f

32. Najaf-Zadeh A, Leclerc F. Noninvasive positive pressure ventilation for acute respiratory failure in children: a concise review. *Ann Intensive Care.* (2011) 1:15. doi: 10.1186/2110-5820-1-15

33. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med.* (1981) 70:65–76. doi: 10.1016/0002-9343(81)90413-7

34. Konrad F, Schreiber T, Brecht-Kraus D, Georgieff M. Mucociliary transport in disease patients with respiratory tract infections. *Am J Phys Med Rehabil.* (2000) 84:83–8; discussion 9–91. doi: 10.1097/01.PHM.0000151941.97266.96

35. Rivera R, Tibballs J. Complications of endotracheal intubation and mechanical ventilation in infants and children. *Crit Care Med.* (1992) 20:193–9. doi: 10.1097/00003324-199202000-00008

36. Tzeng AC, Bach JR. Prevention of pulmonary morbidity for patients with neuromuscular weakness: a new management paradigm. *Chest.* (2010) 137:1033–9. doi: 10.1378/chest.09-2144

37. Simonds AK. Ventilator support in children with neuromuscular disorders. *Pediatr Crit Care Med.* (2012) 13:e161–e170. doi: 10.1097/PCC.0b013e31823888ad1

38. Sancho J, Servera E, Diaz J, Marín J. Efficacy of mechanical insufflation-exsufflation in medically stable patients with myotrophic lateral sclerosis. *Chest.* (2004) 125:1400–5. doi: 10.1378/chest.125.4.1400

39. Lechtzin N, Wolfe LF, Frick KD. The impact of high-Frequency chest wall oscillation on healthcare use in patients with neuromuscular diseases. *Ann Am Thorac Soc.* (2016) 13:904–9. doi: 10.1533/annalsats.201509-5970C

40. Yuan N, Kane P, Shelton K, Matel J, Becker BC, Moss RB. Safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial. *J Child Neurol.* (2010) 25:815–21. doi: 10.1177/0883073809350223

41. Racca F, Vianello A, Mongini T, Ruggeri P, Versaci A, Vita GL, et al. Practical approach to respiratory emergencies in neurological diseases. *Neurrol Sci.* (2012) 33:497–508. doi: 10.1007/s10072-011-0416-3

42. Chen TH, Hsu JH, Jiang YJ. Noninvasive airway approaches for acute neuromuscular respiratory failure in emergency departments. *Pediatr Pulmonol.* (2017) 52:E55–E7. doi: 10.1002/ppul.23693
71. Calderini E, Chidini G, Pelosi P. What are the current indications for noninvasive ventilation in children? *Curr Opin Anaesthesiol.* (2010) 23:368–74. doi: 10.1097/ACO.0b013e32839507b

72. Gay PC. Complications of noninvasive ventilation in acute care. *Respir Care.* (2009) 54:246–57; discussion 57–8.

73. Modi HN, Suh SW, Hong JY, Cho JW, Park JH, Yang JH. Treatment and complications in flaccid neuromuscular scoliosis (Duchenne muscular dystrophy and spinal muscular atrophy) with posterior-only pedicle screw instrumentation. *Eur Spine J.* (2010) 19:384–93. doi: 10.1007/s00586-009-1198-z

74. Carron M, Free U, BaHammam AS, Dellweg D, Guarracino F, Cosentini R, et al. Complications of noninvasive ventilation techniques: a comprehensive qualitative review of randomized trials. *Br J Anaesth.* (2013) 110:896–914. doi: 10.1093/bja/aet070

75. Abudesso C, Nunes P, Silvestre C, Matias E, Loureiro H, Almeida H. Noninvasive ventilation in acute respiratory failure in children. *Pediatr Rep.* (2012) 4:e16. doi: 10.4081/pr.2012.e16

76. Wolfer A, Calderini E, Iannella E, Conti G, Bihan P, Dolcini A, et al. Evolution of noninvasive mechanical ventilation use: a Cohort study among Italian PICUs. *Pediatr Crit Care Med.* (2015) 16:418–27. doi: 10.1097/PCC.0000000000000387

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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