Review Article

Respiratory issues and current management in neuromuscular diseases: a narrative review

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Background and Objective: Respiratory care is often embedded as a component of the overlapping management strategies in many patients with neuromuscular disease (NMD). Implementation of respiratory care strategies requires a sensitivity to the nature of the disease, the vulnerability during rapid eye movement (REM) sleep and complicating comorbidities specific to each patient. Care must adjust to progression of the disease as well as the comfort and preferences of the patient. Clinical presentations are usually heterogenous based on the specific NMD and overall course of the disease making diagnosis and respiratory care challenging. The aim of this review was to review the state-of-the-art evidence-based clinical practices and updates in the management of respiratory complications in patients with NMDs.

Methods: We conducted a search on the PubMed and Medline databases using these keywords: secretions, neuromuscular disease, neuromuscular disorders, non-invasive ventilator, neuromuscular respiratory weakness, respiratory failure. The specified timeframe began from 1980 to 2024.

Key Content and Findings: Timely use of non-invasive ventilation and overall respiratory care is most important as emerging evidence shows some benefits with improved mortality in this group of patients. In some settings, comorbid complications that dictate need for airway management and oral diversion may have a more profound impact on mortality than the effectiveness of ventilatory support that are chosen. A multidisciplinary team approach to care has been shown to improve the quality of life and survival in these patients in centers of excellence. Patients should have the ability to access services provided by neurology, pulmonology, speech pathology, sleep medicine, cardiology and respiratory therapy services.

Conclusions: The cornerstone for management of respiratory failure and sleep disordered breathing in NMD is non-invasive ventilation (NIV). Initiation of this support and other respiratory cares need to be timely, and patients may have very subtle symptoms during the early stages of the disease which makes it challenging in recognizing the onset of respiratory muscle stress and fatigue. Close attention to these symptoms as well as respiratory and radiologic parameters is essential for appropriate incorporation of these cares

Keywords: Neuromuscular disease (NMD); non-invasive ventilation (NIV); neuromuscular respiratory weakness; respiratory failure

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Introduction

While neuromuscular diseases (NMDs) do not directly affect lung tissue, they can affect the muscles involved in breathing, coughing, and laryngeal competence making respiratory complications common in people affected with these disorders (1-4). NMD can impair all three respiratory components: breathing, airway clearance, and airway protection as well as selective disorders that may be modified by position or sleep (5). Given the normal respiratory reserve, dyspnea at rest (a key symptom of breathing impairment) may not be obvious in the initial stages of these disorders and appropriate breathing tests need to be performed for timely diagnosis of inspiratory and expiratory muscular weakness (5).

Sleep disordered breathing (SDB) can present early in the course of the disease. Respiratory failure can result from untreated SDB, thereby increasing the morbidity and mortality in NMD patients (6). Timely use of non-invasive ventilation, control of secretions, prevention of respiratory infections and overall respiratory care are most important as current evidence shows some benefits with improved mortality in this group of patients (3). When and how to incorporate these respiratory cares is perhaps as important if not more than the management of the primary NMD by the neurologist. Given the limited number of dedicated neuromuscular clinics, a simplified but comprehensive review is essential for primary care providers as well as sleep providers who may not have background in pulmonary medicine and take care of this subset of patients. Moreover, there have been new advances and updates in the respiratory care of NMD patients based on emerging scientific data. This review will focus on the evidence-based clinical approach in the management of respiratory issues that arise in adult patients with NMD. We will also discuss the latest advances made in airway clearance and assisted ventilation for these patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1931/rc).

Methods

Literature for this narrative was identified using the following terms in Medline and PubMed: "secretions", "neuromuscular disease", "neuromuscular disorders", "respiratory failure", "non-invasive ventilation", "sleep disordered breathing", "respiratory" and "pulmonary". For the initial search, articles published between 1980 and 2024 were prioritized, including original articles, clinical trials, case series, and reviews. Subsequently, additional articles were retrieved based on manual searches from the references in the literature. Only articles in English (or translated to English) were considered (please see *Table 1*).

Respiratory manifestations of NMD

Dysfunction of the neuromuscular respiratory system can be divided into 3 primary areas of function (see *Figure 1*): (I) swallowing and airway protection, determined by glottic and bulbar muscles; (II) cough, determined by the coordinated expiratory, inspiratory, and glottic function; and (III) ventilatory function, determined by the inspiratory and expiratory muscles (7). There is some heterogeneity with how these functional parts of the respiratory system are affected over the course of disease and across several types and subtypes of NMD (see *Tables 2,3*) (6,8,9).

Assessing respiratory muscle strength

Measurement of respiratory muscle strength is useful to identify respiratory muscle weakness and assess the level of severity. The standard for diagnosing neuromuscular respiratory weakness is transdiaphragmatic pressure (Pdi) which is invasive and usually not clinically applicable. Objective measurements of diaphragmatic weakness include maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and both supine and upright forced vital capacity (FVC) (10,11). Although FVC measurement is widely used (2,3), it may be insensitive to detect early onset of respiratory weakness and correlates poorly with symptoms of nocturnal hypoventilation and hypoxemia (12). Supine FVC may be a better predictor of diaphragm weakness because correlates better with Pdi (12). MIP less than 60 cmH_2O may be more effective in detecting early respiratory weakness than either supine or upright FVC, but it appears to be effort dependent and therefore less reliable. Sniff nasal inspiratory pressure (SNIP) measurements can also be considered for persons unable to achieve an effective seal on the device mouthpiece. SNIP under 40 cmH_2O accurately predicts nocturnal hypoxemia [nocturnal oximetry (ONO)] and may predict increased mortality with less values (10,11). There has been increasing use of ultrasound and magnetic resonance imaging (MRI) to diagnose diaphragmatic weakness and respiratory weakness especially in NMD patients with facial and bulbar involvement. This subset of patients

Table 1 The search strategy summary

Items	Specifications
Date of search	June 30, 2023
Databases	Medline/PubMed
Search terms used	"Secretions", "neuromuscular disease", "neuromuscular disorders", "respiratory failure", "non-invasive ventilation", "sleep disordered breathing"
Time frame	January 1, 1980 to January 30, 2024
Inclusion and exclusion criteria	Inclusion: only studies in English (or translated in English)
	Exclusion: studies lacking enough data were excluded
Selection process	B.A. conducted the initial literature/database search. All authors conducted additional searches

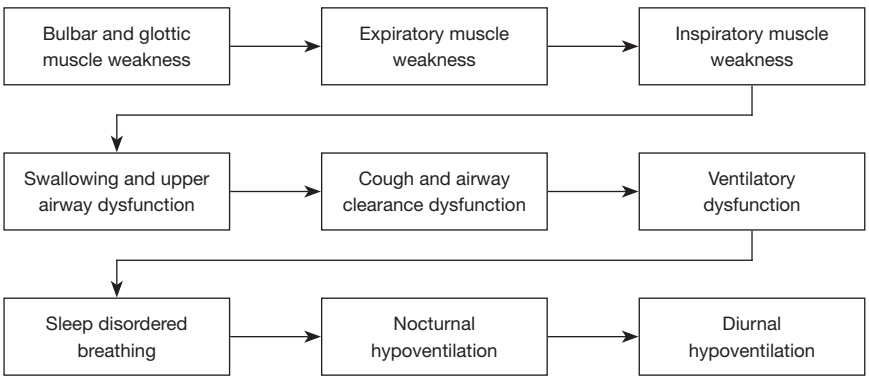

Figure 1 Physiology of neuromuscular respiratory weakness.

Table 2 Classes of neuromuscular diseases

Motor neuron disease	Muscular dystrophies	Non-dystrophic myotonias	Disorders of neuromuscular transmission	Peripheral neuropathies	Metabolic and mitochondrial myopathies	Neuromuscular disorders affecting the thorax
Amyotrophic lateral sclerosis	Becker muscular dystrophy	Myotonia congenita	Myasthenia gravis	Friedreich's ataxia	Lactate dehydrogenase deficiency	Spinal cord injury
Spinal muscular atrophy	Duchenne muscular dystrophy	Periodic paralysis	Eaton-Lambert syndrome	Charcot-Marie tooth disease	Carnitine deficiency	Poliomyelitis and post poliomyelitis syndrome
	Facioscapulohumeral	Myotonia fluctuans	Congenital myasthenic syndrome		Mitochondrial myopathy	Diaphragm paralysis/phrenic nerve injury
	Congenital and myotonic dystrophy				Acid maltase deficiency	
	Oculopharyngeal				Phosphofructokinase deficiency	

Table 3 Signs and symptoms of neuromuscular respiratory weakness

Symptoms	Signs	Testing	Cause
Supine dyspnea	Abdominal paradox	Reduced vital capacity and maximum inspiratory pressure	Diaphragm weakness
Upright dyspnea	Ineffective cough; chest wall paradox	Reduced vital capacity and reduced maximum expiratory pressure	Low cervical spine injury
Excessive sleepiness	Myotonia	Genetic testing	Myotonic dystrophy
	Tachypnea	Reduced VC, MIP	Sleep disruption
	Poor airway clearance	Swallow studies	Hypercapnic encephalopathy
	Morning headaches	Awake and sleep PCO_2	
	Asterixis		

VC, vital capacity; MIP, maximal inspiratory pressure; PCO_2, partial pressure of CO_2.

often has difficulty performing the standard spirometric tests predominantly due to the inability to maintain a sufficient seal over the mouthpiece. Recent studies involving ultrasound measurements of diaphragmatic thickness showed a significant decrease in amyotrophic lateral sclerosis (ALS) patients and the end-inspiratory diaphragmatic thickness and thickening ratio correlated well with %FVC (13-15). Thus, diaphragmatic ultrasound may be a potential alternative to pulmonary function tests in assessing respiratory function in NMD patients since it is not effort dependent and appears to be more reliable (16). There are no definite guidelines as to when or how often these respiratory evaluations should be performed in NMD patients but they need to be considered when available in accordance to regional patterns and performed at a minimum of every 6 months (2,3). A multi-variable approach is needed in these patients to assess neuromuscular respiratory weakness as not a single test can reliably detect the onset of respiratory weakness (3). This requires the use of several diagnostic tools such as pulmonary function tests (PFTs) (FVC, MIP/MEP), ONO or polysomnogram (PSG) to predict the right timing to initiate noninvasive ventilation (NIV) (3). PSGs are valuable for NIV initiation particularly for symptomatic patients in whom their PFTs, arterial blood gas (ABG) and ONO do not meet the threshold for initiation to detect nocturnal hypoventilation. The use of daytime oxygen saturation (SpO_2) is quite limited and may not predict sleep-related oxygen desaturations due to the shape of the oxyhemoglobin dissociation curve. NMD patients can have minor daytime oxygen dissociation whilst having significant nocturnal desaturations particularly during REM sleep (17). An awake SpO_2 <95% in Duchenne muscular dystrophy (DMD) patients may indicate need for nocturnal ventilatory support and further evaluations for hypoventilation need to be considered (1).

Initiation of ventilatory support

NMDs are categorized as restrictive thoracic disorders for reimbursement purposes from the center for Medicare and Medicaid services (CMS) with different criteria for NIV devices (no remote adjustment) *vs.* respiratory assist devices (RADs) (permit remote adjustments with or without back up rate) (see *Figure 2*). The minimum requirement for the initial coverage of respiratory assists devices includes specific measured thresholds (*Figure 2*) while professional guidelines require the presence of signs/symptoms of hypoventilation (*Table 4*) and any of the following (1-3,10,11,17,18), The European guidelines for NMD and ATS guidelines for DMD are less restrictive (*Table 4*). Hypoventilation typically presents initially in sleep particularly during REM sleep and may progress to diurnal hypoventilation. Obtaining transcutaneous CO_2 monitoring (TCM) during PSG can help detect nocturnal hypoventilation in these patients particularly if they have normal PFT and ONO (3). In general, PSGs are not required for initiation in adult patients but may be needed in the pediatric population (1,3). Subjective symptoms such as orthopnea, frequent nocturnal awakenings, excessive daytime sleepiness and morning headaches are used as indicators for initiating NIV in these patients. Several studies have suggested that early initiation of NIV even without overt signs/symptoms of daytime hypoventilation may be associated with a slower decline in respiratory

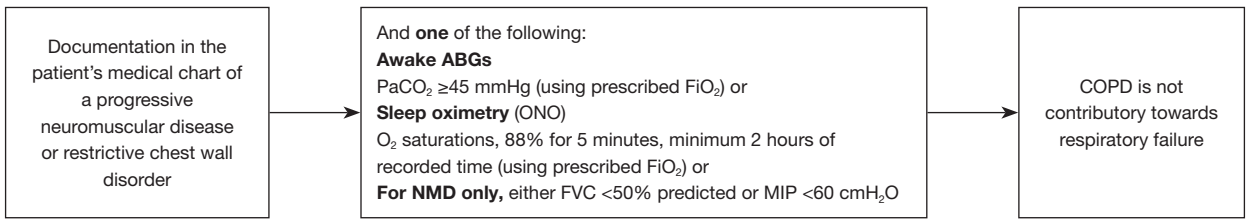

Figure 2 Indication for use of RADs in neuromuscular disease in accordance with CMS guidelines. RAD, respiratory assist device; CMS, Centers for Medicare & Medicaid Services; ABG, arterial blood gases; MIP, maximal inspiratory pressure; NMD, neuromuscular disease; ONO, nocturnal oximetry; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; $PaCO_2$, arterial partial pressure of carbon dioxide; FiO_2, inspiratory fraction of oxygen.

Table 4 Guideline criteria for initiating NIV

ATS/BTS: DMD	ACCP/EFNS: NMD
Use of NIV is indicated with one of the following	Signs and symptoms as in *Table 2* above suggestive of hypoventilation in addition to one of the following
• FVC <30% predicted[†]	• FVC <50% predicted without symptoms or FVC <80% predicted with symptoms (ACCP)
	• FVC <80% predicted (EFNS)
• Sleep study: AHI >10/hour	• MIP <−40 cmH_2O (ACCP)
• $ETCO_2$ >45 mmHg	• ONO: <88% for >5 minutes
• Baseline nocturnal SpO_2 <95% when awake	• Diurnal hypercapnia/daytime PCO_2 >45 mmHg

[†], FVC ≤50% of predicted indicates a higher risk of ventilatory failure and possible need for ventilatory support; FVC <30% increases the need for ventilatory support and urgent referral to respiratory team [BTS (1,2)]. NIV, noninvasive ventilation; ATS, American Thoracic Society; BTS, British Thoracic Society; ACCP, American College of Chest Physicians; EFNS, European Federation of Neurological Societies; DMD, Duchenne muscular dystrophy; NMD, neuromuscular disease; ONO, nocturnal oximetry; FVC, forced vital capacity; MIP, maximal inspiratory pressure; SpO_2, oxygen saturation; PCO_2, partial pressure of CO_2; AHI, apnea hypopnea index; $ETCO_2$, end tidal CO_2.

Table 5 Respiratory symptoms and their presentation in NMD patients—acute versus chronic

Respiratory issues	Acute	Chronic
Ventilatory failure	+	+
Coughing/impaired airway clearance/pneumonia	+	+
Drooling and excessive salivation		+
Vocal cord dysfunction		+

+: possible presentation. NMD, neuromuscular disease.

muscle strength and improved overall survival (19). A prospective study showed that early initiation of NIV in ALS patients postponed the functional decline and the decrease of respiratory muscle strength. In this study, the early NIV group had a statistically significant slower decline in FVC and higher maximal inspiratory pressure (Pimax), emphasizing that perhaps the European guidelines are more appropriate with their less restrictive guidelines (19). This finding was postulated to be because of the respiratory muscle unloading due to NIV use (19). A recent study showed that mortality in NMD patients may be preceded by decreased NIV use and adherence rather than inadequate ventilatory support (20).

In the next section of the article, we discuss the different respiratory symptoms and their presentations—acute versus chronic (see *Table 5*) and the management strategies, with emphasis on SDB and ventilation. Patients seen at the sleep clinics may have undiagnosed SDB, or they are in a stable condition with underlying chronic hypoventilation or seen after being discharged from hospital after receiving treatment for acute respiratory failure.

Table 6 Different modes of bilevel positive airway pressure devices and ventilators

PAP modality	Description
Spontaneous timed	Bilevel positive airway pressure ventilation (pressure support is determined by difference between prescribed IPAP and EPAP), patient triggered, and flow cycled, with a back-up breath which is timed if an apnea period occurs or patient's intricate respiratory rate is less than prescribed rate
Spontaneous	Bilevel positive airway pressure, patient triggered, flow cycled. However, there is no back up rate
Volume assured pressure support (AVAPS versus iVAPS)	Prescribed average assured tidal volume, normally based on patient's ideal body weight (8–10 mL/kg) which is delivered between a range of upper and lower settings of IPAP and a fixed EPAP. Pressure support may vary based on the difference between variable IPAP and fixed EPAP
Volume assured pressure support—auto-EPAP (AVAPS-AE versus iVAPS-AE)	Prescribed average assured volume, normally based on patient's ideal body weight (8–10 mL/kg) which is delivered between a range of upper and lower settings of IPAP as well as upper and lower settings of EPAP
Pressure control	Prescribed IPAP and EPAP settings, with a prescribed inspiratory time. Delivered volume is based on compliance of the lungs. All breaths are timed
Proportional open ventilation (Life2000 Ventilator)	Venturi-effect technology allows higher volume delivery (up to 2,000 mL) with portable/wearable device. Ventilation is variable based on activity levels/effort and entrained air via interface

IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; AVAPS, average volume assured pressure support; iVAPS, intelligent VAPS; AE, auto-EPAP.

Respiratory failure

Chronic ventilatory support

NIV has become a routine practice worldwide in management of chronic respiratory failure (21). The use of mechanical ventilation (IMV) in NMD patients, particularly ALS, varies considerably based on geographical location. In the United States and Europe, the utility rates vary from 5% to 10% (22,23). This can also vary based on gender (24). It has been reported that increased use of NIV with MPV is associated with decreased utilization of IMV (25).

In NMD patients, NIV support devices can be provided with bi-level positive pressure RADs, or multi-modal NIV devices with multiple options including assured volume (tidal volume or alveolar ventilation) (see *Table 6*).

With pressure support (PS), every breath is triggered by the patients, and is flow cycled. Triggers have traditionally been assessed with a pressure or flow change to initiate inspiration. Pressure control has the added features of a minimum set rate and fixed inspiratory time. Traditional bi-level positive airway pressure (PAP) devices usually have a fixed inspiratory PAP and expiratory positive airway pressure (EPAP) with a back-up rate and are less frequently used compared to more advanced modalities. RADs are pressure-supported, flow-cycled, bilevel devices which may have additional features of volume-assured pressure support (VAPS), back-up respiratory rate, and inspiratory time control. RADs and NIV are portable and can provide a better quality of life compared to invasive ventilators with tracheostomy (home mechanical ventilators). Different manufacturers use different proprietary algorithms to guarantee the preset tidal volumes and/or minute ventilation. RADs are not life-supporting devices as they do not have a battery pack as in life support devices (26). The latter may be needed when RADs are not able to achieve tidal volumes or minute ventilation and when consistent daytime ventilation is needed.

In choosing the initial settings for pressure-supported bilevel NIV, the addition of average volume assured ventilatory support (AVAPS) or intelligent VAPS (iVAPS) modes guarantees the minute ventilation or alveolar exhaled tidal/alveolar ventilation respectively and work in the self-adjusting pressure mode, which is an excellent option for NMD patients with progressive disease as respiratory support needs increases with time (26). ALS patients may have rapid changes in ventilatory requirements and breathing pattern changes during the course of the disease compared to non-ALS patients (20). Target tidal volume is 6 to 8 mL/kg ideal body weight or can be predicted by normative tables and should be adjusted proportionally in patients with concomitant fixed restriction from lung resection, chronic obstructive lung disease, parenchymal, pleural or chest wall restriction. EPAP is often set as low as possible in patients with NMD, particularly with bulbar symptoms to ensure tolerance and maximize range of ventilatory support (PS) (17). Pseudo-central events and not

true upper airway obstruction are usually the most common cause of alveolar hypoventilation and desaturations in these patients and tend to occur first during REM sleep (9). Alveolar hypoventilation then progresses to other sleep stages and eventually becomes diurnal. The main purpose of EPAP in these patients is to address rebreathing of CO_2 in the single inspiratory circuits by flushing out. If there is concomitant obstructive sleep apnea (OSA), EPAP can be titrated accordingly. Control of inspiratory time (Ti) is essential in any NIV mode selected to address rapid shallow breathing associated with reduced spontaneous cycling. Ti is usually set greater than 1.2 seconds (17). The shallow breathing index (f/Vt) is a reliable surrogate for work of breathing and should usually be <50 (17). A retrospective study showed that while ineffective triggering might be addressed by using a set backup rate, it does not address rapid shallow breathing associated with reduced spontaneous cycling. Thus, the use of a device that ensures sufficient inspiratory time as well as providing a guaranteed back-up rate is necessary to support effective NIV in this group of patients (27). Newer devices have a proprietary adaptive algorithm (Auto-Trak) which automatically adjusts triggering and cycling while compensating for leaks to ensure patient's synchrony and comfort, without requiring manual adjustments. A study suggested that VAPS provides a more reliable goal Vt than does PS and is associated with decreased f/Vt (27). The other advantages of using VAPS include improvement in sleep quality and respiratory muscle strength. The use of adaptive servo-ventilation (ASV) is not appropriate for NMD patients as it guarantees flow but not tidal volume/minute ventilation in these patients.

Interface

The interface distinguishes NIV from invasive ventilation. They include nasal mask, nasal pillow mask and oronasal ventilation [full face mask versus hybrid masks (nasal pillow mask with oral mask)]. Mouthpieces can also be used, usually on demand through sip ventilation during the day. Regardless of the type of mask selected, it is important to optimize fit and comfort and ensure that straps have the right amount of tightness to minimize leaks but without compromising comfort. There are many challenges to ensuring a well-fitting mask in NMD patients particularly with facial muscle wasting. Masks may need to be adjusted or changed as younger patients grow and mature due to poor facial development (28). Pediatric masks can be used with adult patients to ensure a good seal and chin straps can be used with nasal pillows to keep the mouth closed. Oronasal mask can paradoxically cause posterior displacement of the tongue leading to increased upper airway resistance (29). Some clinicians will prefer to avoid oronasal mask initially for this reason. A study showed no difference in NIV tolerance between oronasal and nasal masks in NMD patient (30). Masks without a nose hose (hose connection at the scalp region) can also help with comfort particularly in claustrophobic patients allowing for better field of vision and need for mask repositioning during sleep (31).

Desensitization to masks helps with improved comfort and tolerance. and can be achieved by trying several masks without NIV and then using with NIV with a slow escalated air pressure from the device (32).

Day/mouthpiece ventilation (MPV)

With progressive respiratory muscle weakness, there may be a need for ventilatory support during the day. This is usually the case when a person needs more than 16 hours of NIV use per day and consideration should be given to the introduction of mouthpiece (also called sip or demand) ventilation. MPV allows for eating and drinking, facilitates speech/airway clearance with breath stacking, and reduces the need for invasive ventilation (3). There is also reduced risk of skin breakdown by reducing time spent with a mask interface. MPV is more easily used in volume-cycled devices for breath stacking, however, the newer VAP devices have dedicated modes for breath stacking allowing for sip ventilation. The flow-interruption trigger of sip ventilation does not require active inspiratory effort and therefore can be used even in very weak patients (33,34). The mouthpieces can be attached via a malleable arm to motorized wheelchair allowing for use with patients with restricted mobility. MPV can be used to delay the transition or need for mechanical ventilation (3). MPV use may be limited in NMD patients with bulbar symptoms due to poor mouth seal and resultant high leak. An approach with different mask interfaces alternated between day and night use (e.g., oronasal alternating with nasal pillows) to minimize skin breakdown may be used in these subsets of patients (17).

Another evolving area is the use of the Life2000 Ventilator. This is a very portable, wearable, light, mask-free NIV that is designed to provide breathing support to patients as they go about their activities of daily living, particularly those who can walk and are not limited to a wheelchair. It can provide up to 2,000 mL of tidal volume

Table 7 Contraindications to NIV in acute neuromuscular respiratory failure

Cardiopulmonary arrest
Severe encephalopathy
Upper gastro-intestinal bleeding
Hemodynamic instability
Unstable arrhythmias
High aspiration risk
Facial muscle weakness
Significant mucus plugging

NIV, non-invasive ventilation.

(via venturi effect) with different ventilation modes including assist control. Its benefit may be limited in NMD patients with limited mobility. This is very valuable for patients with primarily diaphragmatic weakness and relative sparing of limb muscles such as high spinal injury.

Invasive mechanical ventilators (IMVs)

As a result of improvements in quality of life, survival benefit achieved with NIV and use of MPV, only a small subset of progressive NMD patients will elect to have a tracheostomy and intermittent mandatory ventilation (22,23). Endotracheal intubation may be needed in an acute setting and tracheostomy may be needed while the patient recovers from the acute illness or event causing worsening respiratory failure (34-36). Evaluations should be given for possible decannulation and liberation back to a mask interface after the acute event has resolved. A recent study showed that use of NIV during the day and night is also effective in improving survival and preserving the lung function (33). For others, the need for IMV arises due to the progression of NMD, NIV intolerance, repeated respiratory infections, recurrent aspirations and worsening bulbar function (1,3). Discussions with regards to IMV should be introduced very early in the course of the disease and should include insights to goals of care. Caregivers must be notified of the significant increase in responsibilities compared to NIV and the need for institutionalization (3).

Acute neuromuscular respiratory failure

Acute failure in the setting of NMD can be life threatening and may be the initial presentation leading to a new diagnosis or a complication of a previously known NMD. Acute respiratory failure may be due to exacerbation of neurological disease (e.g., myasthenia gravis) or a complication (e.g., acute stridor, heart failure, pneumonia) (37). Early detection of acute respiratory failure in NMD patients may be difficult since respiratory distress may not be evident. Tachypnea, increased cough and work of breathing may be absent due to the underlying bulbar dysfunction and muscular weakness. Alteration in mentation and paradoxic breathing especially when supine may be more helpful with identification. Serial ABGs may help provide a trend for respiratory failure after ventilatory support has been instituted. However, acidemia and hypercapnea are usually indicative of severe respiratory failure and may not be reliable indicators for initiating ventilatory support (38).

Pulse oximetry is recommended for continuous monitoring but is not very reliable for early detection due to the hyperbolic nature of the oxygen saturation curve (39). Initial evaluation usually requires identifying patients in need of ventilatory support whether NIV or IMV. NIV with oronasal mask is usually preferred except if there are contraindications to its use (see *Table* 7), expectation for prolonged ventilatory support or expected worsening respiratory failure due to type of NMD. Attention needs to be placed on recognizing upper airway obstruction due to posterior displacement of the tongue which can be mitigated by increasing EPAP (40). Indications for ventilator support/intubation are quite different from other causes of acute respiratory failure. Bedside spirometric evaluation is valuable in evaluating pulmonary function and can be used in the determination of need for ventilatory support and assessment of the trajectory of respiratory capacity. Measured values of FVC <20 mL/kg, MIP >−30 cmH_2O and significant reduction from baseline are usually used to determine initiation of ventilatory support (38,41). These criteria are derivatives from observational and retrospective data in myasthenia gravis and GBS patients (42). These parameters may be difficult to obtain in ALS patients due to difficulty making a good seal on the mouthpiece. Although NMD patients may have chronic respiratory failure already on NIV; however, an acute on chronic respiratory failure usually in the setting of pneumonia will require intubation with MV. Criteria for weaning ventilatory support and liberation from MV is not different from other causes of respiratory failure. Additionally, MIP >−50 cmH_2O and significant increase in FVC are indicators for successful liberation from ventilatory support in acute neuromuscular respiratory failure (43). During hospitalization for

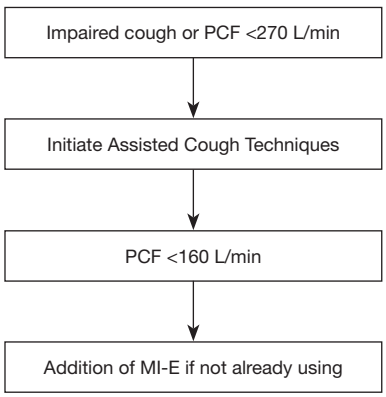

Figure 3 Management of impaired airway clearance. PCF, peak cough flow; MI-E, mechanical insufflation-exsufflation.

acute respiratory failure, the goals of care and patient's wishes would need to be addressed. Some patients have advanced directives which will need to be re-evaluated and updated (1). Tracheostomy use during such admissions needs to be discussed with the respiratory neuromuscular team or specialty team experienced in the management of these patients (2). The focus of management may change to comfort measures during these hospitalizations based on these discussions and trajectory of acute illness (1). DMD patients are usually on long-term corticosteroids and have an increased risk for adrenal suppression. Stress dose steroids, which is usually hydrocortisone, should be considered (44).

Impaired airway clearance

Cough effort physiology is complex and involves a coordinated expiratory, inspiratory, and glottic function. A deficit in any of these steps will lead to ineffective cough. Patients with NMD often have difficulty clearing secretions because of vocal cord dysfunction and or inadequate cough. Neuromuscular activity and effective coordination can be measured by assessing peak cough flow (PCF), which is the maximum expiratory flow generated after a forceful effort. A PCF of above 160 L/min is required for an effective cough and values less than 270 L/min are associated with increased mucus retention, increased risk of infection and hospitalizations (45). Assisted airway clearance involves two main aspects—cough augmentation and sputum mobilization (see *Figure 3*) (46,47).

Cough augmentation techniques include glossopharyngeal breathing, breath-stacking with or without mouthpiece, manually assisted cough and device-assisted cough augmentation. Cough augmentation is most effective when assistance is provided during the inspiratory and expiratory phases. Lung volume recruitment (LVR) with glossopharyngeal breathing may be appropriate for NMD patients with hypoventilation and can be performed independently with minimal assistance (3). The use of LVR with a handheld bag or mouthpiece requires caregiver assistance and may be difficult to perform for my patients alone. Manually assisted cough is more effective when added to LVR.

When the above techniques are not effective, adding a mechanical insufflation-exsufflation (MI-E) device (cough assist device) may be helpful but they may be associated with increased cost (3). MI-E is the most effective and most utilized mechanical cough augmentation technique (46,47). This involves generation of a positive pressure-limited insufflation in the lung during the inspiratory phase followed by a quick reversal to negative pressures during the expiratory phase, leading to the generation of expiratory flow sufficient to clear secretions (47). LVR, done at least twice daily, has been shown to slow the rate of lung volume decline in DMD and systemic muscular atrophy (SMA) (47,48). These pressures are adjusted to achieve a PCF of more than 160 L/min. The minimal effective pressures for most individuals are inspiratory pressure of +30 cmH_2O and expiratory pressure of –30 cmH_2O, with NMD patients usually requiring pressures of +40/–40 cmH_2O to achieve their target PCF (49). Patients with bulbar involvement may have a paradoxical laryngospasm and may require lower adjusted pressures (50). Some of the newer cough assist devices (MI-E-CoughAssist T70® and Synclara cough systems) have proprietary algorithms which give patients the ability to initiate their therapy by triggering on patient's inspiration and also add other functionality such as high frequency oscillations (50). This feature helps to synchronize therapy with the breathing pattern and is a more comfortable, natural treatment. Other devices (e.g., VOCSN®) have multi-functionality that combines several respiratory therapies including cough assist, nebulization, oxygen delivery as well as ventilation (51). The combination of the cough augmentation techniques can further improve the target peak expiratory flow (PEF) rates. A randomized crossover single-center controlled trial with 40 subjects with NMD and respiratory muscle dysfunction showed that MI-E used in conjunction with manual thrust improved PCF even further compared to MI-E alone (49). Without access to cough augmentation devices or with PCF >160 L/min,

pairing manual breath stacking maneuvers using a bag-valve mask with manually assisted cough can also achieve target PEF rates (3,52,53).

Sputum mobilization with high-frequency oscillatory ventilation can be used to reduce mucus impaction, recurrent respiratory infections, and hospitalization (54). This uses rapid changes in positive and negative pressure causing oscillatory motion which helps thin and loosen thick mucus usually in the smaller airways (54). They are also valuable to NMD patients who are unable to participate in cough augmentation (54-56).

Pneumonia usually occurs in the setting of dysphagia (aspiration pneumonia) and difficulty in mobilizing pulmonary secretions (55). This may result in hospitalizations and acute respiratory failure. The presence of pneumonia lowers the threshold for intubation since bronchoscopy with airway clearance may be beneficial due to the presence of a secured airway.

Vocal cord dysfunction

Symptoms of vocal cord dysfunction include hoarseness, hypophonia, intermittent nocturnal inspiratory stridor and dyspnea. Vocal cord dysfunction has a prevalence of about 4% (57) while stridor was identified in up to one-third of patients with multisystem atrophy (MSA). Early stridor has been associated with sudden death and a poorer survival rate (58,59). Another study revealed that MSA patients treated for stridor by either tracheostomy or continuous positive air pressure (CPAP) had a longer median disease duration than those without treatment. Reducing the upper airway resistance through the application of PAP has been found to be successful in the treatment of nocturnal stridor although there is a risk of respiratory failure in the setting of a marginal airway (60,61). Successful use of antispasmodic agents like benzodiazepine has been described in literature and may be a reasonable first step (62). Treatment of severe airway compromise usually involves acute airway management and cricothyroidotomy may be necessary if there is difficulty with intubation.

Drooling and excessive salivation

Sialorrhea is a frequent problem in NMD patients and is caused by difficulty in saliva clearance or hypersecretion of saliva. Poor clearance results from bulbar dysfunction, poor oral and facial muscle control. Sialorrhea causes a range of physical and psychosocial complications, including lip cracking, dehydration, odor, and social stigmatization, all of which can be problematic for NMD patients and their caregivers. Treatment of sialorrhea is best managed with a multi-disciplinary approach that includes pulmonologists, speech pathologists, occupational therapists, and otolaryngologists. Treatment options range from conservative measures (i.e., observation, postural changes, biofeedback), medications to more aggressive options such as radiation, and surgical therapy (see *Figure 4*). Anticholinergic medication includes topical atropine, oral hyoscyamine sulfate, nebulized or subcutaneous glycopyrrolate, oral amitriptyline, scopolamine patches and are the first line treatment and are effective in reducing drooling, but their use may be limited by debilitating side effects (63). Glycopyrrolate is preferred due to a better side effect profile because of its inability to cross the blood-brain barrier and it is relatively cheaper. Anticholinergic drugs are not effective in a subset of treated patients. In the long term, these medications are often not a sustainable therapy for sialorrhea in a great number of patients (64,65). The injection of botulinum toxin type A into the parotid and submandibular glands is safe and effective in controlling refractory drooling and can be used as a 2nd line agent, but the effects fade after several months (3.5 months on average), and repeat injections are necessary (2,3,66-70). Botulinum injections can cause reduction in oropharyngeal function which can be challenging for bulbar NMD patients.

External beam radiation with photon- or electron-based therapy can be used in refractory cases of sialorrhea with lasting benefits. Electron-based therapy is preferred due to better precision compared to photon-based therapy (64,65,70). Radiation may be an excellent option for refractory drooling in patients with bulbar symptoms as there is preservation of the oropharyngeal function. Patients should be made aware of mucositis as a potential side effect of radiation (64,71).

Surgical intervention, including salivary gland excision, salivary duct ligation, and duct rerouting, provides the most effective and permanent treatment of significant sialorrhea and can improve the quality of life of patients and their families or caregivers. Ablative therapy of an isolated salivary gland may not be effective due to compensatory hypersecretion from the other salivary glands (72).

Diaphragmatic pacing

Diaphragmatic pacing is the use of electrical stimulation

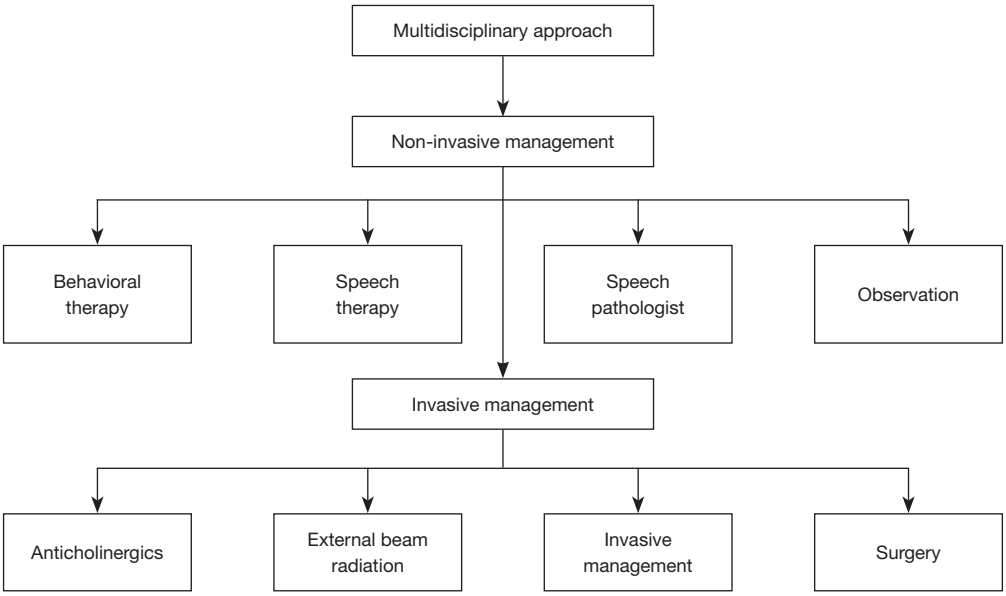

Figure 4 Management of drooling.

to the phrenic nerves to cause diaphragm contraction. This has been used in select individuals with chronic respiratory failure who have an intact phrenic nerve function but an inadequate central drive (e.g., congenital central hypoventilation syndrome) or during the recovery period from a high-level spinal cord injury (73,74). An intact phrenic nerve is vital for the success of this treatment option. Two recent studies showed that diaphragmatic pacing can be an alternative treatment to using mechanical ventilation in these groups of patients (74,75). While diaphragmatic pacing has been used in select cases of NMD, the consensus and recent studies have not shown any clear survival benefit in NMD and may be harmful (76-78).

PSG

Medicare guidelines do not require PSG for initiation of NIV. Patients with NMD are usually treated with NIV without a formal PSG assessment based on current guidelines (3,7). The most common SDB in NMD is probably REM-related hypoventilation usually due to diaphragmatic weakness. This is usually first noticeable in REM sleep when NMD patients are most vulnerable to the physiologic changes in sleep. This is usually due to pseudo-central apneas which are commonly misdiagnosed as obstructive events (9). For this reason, PSG may be helpful in assessing the need for NIV in symptomatic patients when they have normal PFTs and ONO tests (3). PSG with titration studies may help identify the type of SDB and help with establishing the right amount of EPAP required to overcome any upper airway obstruction if present. Using TCM during the titration studies is helpful in adjusting the NIV settings. However, the newer NIV devices have an auto-titrating EPAP mode which can help treat concomitant OSA without the need for titration studies. NMD patients with concomitant SDB are usually managed with NIV using the AASM guidelines whereas the ERS guidelines may be more applicable to pediatric patients (3).

Tele-monitoring

Current-generation NIV devices can monitor and track several parameters including duration of daily usage. These parameters are stored and allow the clinician access remotely by modem (see *Table 8*) and adjust remotely if RADs is being used. This is advantageous for patients in rural settings. Usually, NIV doesn't allow for remote adjustments by the clinician and adjustments can be made with the help of the assigned respiratory therapist. This is also valuable for telemedicine clinic visits. Some studies have suggested that in NMD such as ALS or MD, there is a clear correlation between device adherence and survival therefore it is imperative that any barriers to use are quickly identified and resolved. Blood gas monitoring and ONO

Table 8 Telemonitoring and possible adjustments of RADs and NIVs

Device download data	Troubleshooting
Rapid shallow index [f/VT >50]	Check for leaks
	Increase the pressure support
	Increase the minimal inspiratory time
Length of use	<4 hours: reduce pressures with bulbar patients, check for device desynchrony
	>16 hours: consider mouthpiece ventilation, use of Life2000 Ventilator (limb sparing weakness and able to walk) or alternating different types of masks
Increased leakage	Mask fitting
	Switch to pediatric mask if there is orofacial wasting
Inadequate exhaled tidal volume	Check for mask leaks
	Increase pressure support
Low spontaneous breath cycling (%SpC)	Increase the minimal inspiratory time usually >1.3 seconds
Ineffective triggering	May increase back up rate for increased ventilator support; check for air trapping (reduced pressure support if present or increase EPAP) and increase trigger sensitivity in advanced disease
Residual apnea hypopnea index	Not usually an issue with most NMD patients. Residual AHI may be due to pseudo-central events and not obstructive. May consider PSG to better evaluate sleep disordered breathing. Avoid aggressive EPAP adjustment which may increase intolerance

RAD, respiratory assist device; NIV, noninvasive ventilation; EPAP, expiratory positive airway pressure; NMD, neuromuscular disease; PSG, polysomnogram; SpC, spontaneous breathing cycle.

are particularly helpful during outpatient visits.

Future areas of research

Current parameters for diagnosing and monitoring respiratory muscular weakness in NMD patients are laborious, cumbersome, scarce and time consuming. Development of serum biomarkers and radiologic evaluations which correlate well with respiratory muscular weakness and diaphragmatic dysfunction will be immensely helpful for timely and effective management of respiratory neuromuscular weakness. Right now, further research is needed to further elucidate how these can be incorporated into the comprehensive care of these patients.

Conclusions

NMDs are a group of diseases that can lead to SDB and ventilatory failure usually involving respiratory muscle stress predominantly in the diaphragm. There can also be bulbar involvement resulting in recurrent respiratory infections. Clinical presentations are usually heterogenous depending on the type of NMD and clinical course which makes it difficult to have a homogenous approach in the management of these patients. The cornerstone for management of respiratory failure and SDB in NMD is NIV. Initiation of this support and other respiratory cares need to be timely, and patients may have very subtle symptoms during the early stages of the disease which makes it challenging in recognizing the onset of respiratory muscle stress and fatigue. Close attention to these symptoms as well as respiratory and radiologic parameters is essential for appropriate incorporation of these cares. The current use of these parameters is cumbersome and there is a need to conduct randomized studies and analyze the use of serum biomarkers to determine the onset of respiratory failure and SDB in these patients.

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Footnote

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