Almost one-quarter of the way through the twenty-first century, survival for patients with neuromuscular disorders (NMD) has exponentially increased, in large part because of advancing technologies for noninvasive ventilation (NIV) and airway clearance. Median survival for persons with spinal-onset amyotrophic lateral sclerosis (ALS) has increased from 2 to 24 months after onset of respiratory failure with the use of NIV and airway clearance. Median survival for bulbar-onset ALS has also increased, from 4 to 12 months after onset of respiratory failure.\(^1\) Dramatic increases in median survival have also been seen for individuals with both muscular dystrophies and spinal muscular atrophy (SMA),\(^1,2\) also greatly impacted by the introduction of appropriate respiratory support.

Increased survival is dependent on timely recognition of the onset of respiratory decline, quantification of respiratory muscle function, and introduction of appropriate respiratory assistive devices (RADs) based on disease stage. Care for people with such complex conditions requires buy-in for these often time-consuming interventions and a team approach from the patient and caregiver and a multidisciplinary team that includes experienced respiratory therapists and a pulmonologist. This review focuses on the appropriate recognition of the stages of respiratory decline in chronic NMD and the disease stage-specific interventions to maintain respiratory function.

**Physiology of Respiratory Failure**

NMD affect muscle function via loss of central drive, loss of function at the neuron or neuromuscular junction, or muscle fiber destruction. Loss of function at any of these levels impacts the muscles of respiration, causing impaired airway clearance due to weakened or absent cough, hypoventilation with hypoxia and hypercapnia, and ultimately overt respiratory failure. Onset and progression of respiratory failure can be acute (eg, during a myasthenia gravis [MG] crisis), very gradual (eg, muscular dystrophy), or rapidly progressive (eg, in ALS).

Dysfunction of the neuromuscular respiratory system can be divided into 3 main areas of function: 1) ventilatory function, determined predominantly by the inspiratory muscles; 2) cough function, determined by inspiratory, expiratory, and glottic function; and 3) swallowing and airway protection, determined by glottic muscles.\(^3\) NMD affects each of these functional parts of the respiratory system over the course of disease, which contribute both independently and in concert to result in respiratory failure (Figure).

As muscular weakness progresses, alveolar hypoventilation, oxygen desaturation, and hypercapnia occur.\(^4,5\) Expiratory muscle weakness presents early in respiratory decline and leads to ineffective cough, with resultant atelectasis, poor airway clearance, and an increased risk for pneumonia.

**CLINICAL GEMS**

All patients should have engagement with a multidisciplinary team approach to respiratory support, including participation of neurology, pulmonology, and respiratory therapy, at a minimum.
Inspiratory muscle weakness leads to a decrease in tidal volume, micro- and then macroatelectasis, leading to hypoxia caused by ventilation and perfusion mismatch, and ultimately the development of hypercapnia and respiratory failure. Lastly, weakness of the bulbar muscles because of lost glottis closure limits the ability to clear airway secretions, swallow, and speak, increasing the risk of aspiration. Bulbar dysfunction may contribute to earlier development, or worsening, of sleep-disordered breathing due to upper airway obstruction.

Recognizing the early symptoms of impaired respiration is key to timely objective testing and intervention. Early symptoms of respiratory muscle weakness can include a soft breathy voice, slurred speech, inability to cough or weakened cough, inability to blow the nose, fatigue, morning headaches, daytime somnolence, and cognitive impairment. Recurrent treatment for pneumonia should also prompt consideration of impaired airway clearance or dysphagia. Drooling may be present with early bulbar involvement, due to oropharyngeal dysmotility.

**Assessing Respiratory Muscle Strength**

Objective measurements of respiratory muscle function include maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and both supine and upright forced vital capacity (FVC). The American Thoracic Society consensus statement for the respiratory care of a person with Duchenne muscular dystrophy (DMD) recommends measurements of FVC, forced expiratory volume in 1 second (FEV1), MIP, MEP, and peak cough flow at each visit. CO₂ tension through capnography, transcutaneous CO₂ monitoring, or venous blood sample should be obtained to assess for alveolar hypoventilation in advancing disease or refractory symptoms. Similar recommendations have been made for people with ALS and other NMD.

Importantly, multiparameter testing is needed to fully evaluate these individuals. Although FVC measurement is the most commonly used objective test and is a significant predictor of survival, it may be insensitive to early decline and correlates poorly with symptoms of nocturnal hypoventilation and desaturation. Supine FVC may be a better predictor of diaphragm weakness because it more closely approximates transdiaphragmatic pressure (Pdi), but can be more difficult to obtain. MIP less than 60 cm H₂O and nocturnal oximetry may be more effective in detecting early respiratory insufficiency than either supine or upright FVC and should be considered for those who are symptomatic, with FVC greater than 50% predicted. 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 cm H₂O accurately predicts nocturnal hypoxemia and less than 30 cm H₂O predicts 3-month mortality, although the predictive power for hypoventilation is absent in bulbar ALS.

**CLINICAL GEMS**

All people with systemic neuromuscular disorders should have their respiratory muscle function assessed every 3-6 months.

**Staging Respiratory Decline**

More than physiologic categorization, staging progressive respiratory muscle weakness and loss of function allows for the use of evidence-based practice recommendations for the implementation of RADs. In the Canadian Alternatives in Noninvasive Ventilation (CANVent; available at https://canventottawa.ca) program, stages are defined by objective measures of respiratory muscle strength. At stage 1, there are no respiratory symptoms or overt abnormalities in the initial respiratory function testing. Individuals at stage 1 can also be characterized as asymptomatic, and ideally are referred to pulmonology at this point. At stage 2, overt expiratory muscle weakness has developed, and objective measurements such as a reduction in peak cough flow (<270 L/min) or a maximal expiratory pressure under 60 cm H₂O require initiating lung volume recruitment and assisted airway clearance techniques. At stage 3, there is progressive expiratory muscle weakness and overt inspiratory muscle impairment (FVC <50% in the American Academy of Neurology [AAN] guideline, <80% in the European Federation of Neurological Societies guidelines [EFNS]), or MEP less than 40 cm H₂O. Progression to stage 4 is defined by dependence on 24-hour NIV or invasive mechanical ventilation (IMV). We review RADs in the order they are required by these stages (Table 1).

**Stage 2: Impaired Airway Clearance**

Cough effort physiology is complex and involves responsiveness to cough receptor impulses, phrenic nerve conductio to the diaphragm, glottic closure, and inspiratory and expiratory muscle involvement. A deficit in any of these steps will lead to a reduction in the peak expiratory flow rate during forced exhalation. Assisted airway clearance is required when the peak cough expiratory flow rate drops below 270 L/min. Peak expiratory flow rates below this threshold predict an acute drop in expiratory flow rates below the minimum effective rate of 160 L/min during illness. Peak expiratory flow rates of less than 160 L/min are associated with atelectasis, mucus plugging, respiratory tract infection, and hospitalization, which are the predominant causes of morbidity and mortality in NMD.

The 2 pillars of assisted airway clearance include proximal airway clearance (ie, cough augmentation) and peripheral airway clearance (ie, sputum mobilization). Proximal airway clearance, or cough augmentation, is critical in those who have a weak cough due to neuromuscular weakness.
Proximal airway clearance is most effective when assistance is provided for both the inspiratory and expiratory phases.16 The mechanical insufflator-exsufflator (MI-E) device is the most effective and most commonly utilized cough augmentation technique. The inspiratory insufflation functions as a lung volume recruitment maneuver, optimizing the muscle length-tension relationship to maximize elastic recoil during exhalation. Lung volume recruitment, done at least twice daily, has been shown to preserve vital capacity and slow the rate of lung function decline in DMD and SMA.17,20 Data are less robust in ALS, in which there FVC improves, but without sustained response.21,22 During the exhalation phase, negative pressure is applied to increase the expiratory flow rate. Inspiratory and expiratory pressures are adjusted to achieve a peak cough flow of more than 160 L/min. The minimal effective pressures for most individuals are inspiratory pressure of +30 cm H2O and expiratory pressure of −30 cm H2O, with most requiring pressures of +40/−40 cm H2O to achieve the expiratory cough flow target of 160 L/min. People with predominantly bulbar involvement may have a paradoxical laryngospasm during either the insufflation or exsufflation phase and require significant adjustments.23 For those without access to a mechanical cough augmentation device, pairing manual breath stacking maneuvers using a bag-valve mask and manually assisted cough can also achieve target peak expiratory flow rates; this technique, however, is more labor intensive and caregiver dependent.

Peripheral airway clearance, or sputum mobilization, is usually done with high-frequency chest wall oscillation or intrapulmonary oscillation. Data and clinical practice guidelines are conflicting regarding the benefits of sputum mobilization, although it may have a role concurrent with cough augmentation in persons with acute respiratory illness and those who cannot participate with cough augmentation.24,25

### Stage 3: Nocturnal NIV Support
The need for ventilatory assistance develops during stage 3 and is marked by worsening respiratory muscle weakness and symptoms related to hypoventilation, initially presenting during sleep. Recognition of progressive respiratory insufficiency allows the introduction of elective outpatient nocturnal NIV with ongoing airway clearance in a controlled manner, to prevent respiratory crisis, hospital admission, and the need for urgent IMV. The use of NIV at this stage has been shown to slow the rate of decline in FVC, improve quality of life, and increase survival.26,28

There are several clinical guidelines with recommendations for when to consider and initiate NIV in NMD (Table 2).8,9,29 Supplemental oxygen should not be prescribed to treat sleep-related hypoventilation without ventilatory assistance, because this will mask progressive atelectasis.7 Several ventilatory support devices can be utilized including bilevel positive airway pressure devices, RADs, and IMV. RADs are pressure-supported, flow-cycled, bilevel devices that may have additional features of volume-assured pressure support (VAPS), back-up respiratory rate, and inspiratory time control. Different manufacturers use different proprietary algorithms to deliver the volume-assured pressure support to guarantee a minimum per minute ventilation. RADs are not life-support devices and do not have an internal or external battery, which limits mobility for people using the device. The use of RADs is limited to early disease when only nocturnal ventilation is needed, and inspiratory pressures required to achieve target tidal volume are 25 cm H2O or less. When a person needs more than nocturnal ventilation, inspiratory pressure required to achieve the target tidal volume exceeds 25 cm H2O, or multimodal ventilation strategies are needed, a life-support ventilator is required.

In choosing the initial settings for pressure-supported bilevel NIV, the addition of average VAPS (AVAPS) or intelligent

| Table 1. Indications for Respiratory Assistive Devices and Interventions by Disease Stage |
|---|---|---|---|
| **Stage** | **Risk Assessment** | **Clinical Parameters** | **Interventions** |
| 1 | No risk of respiratory complications | Asymptomatic | Referral to pulmonary specialist |
| 2 | At risk for respiratory complications | Forced vital capacity >50% predicted Peak cough flow <270 L/min Maximal expiratory pressure <60 cm H2O | Assisted airway clearance and mechanical insufflator-exsufflator or breath stacking with manually assisted cough |
| 3 | Progression | Forced vital capacity 50%-80% of predicted | Goals of care discussions |
| 4a | Respiratory insufficiency | Upright or supine forced vital capacity <50% of predicted Peak cough flow <270 L/min Maximal inspiratory pressure <60 cm H2O Daytime partial pressure CO2 >45 mm Hg | Nocturnal noninvasive ventilation (NIV) with/without intermittent daytime NIV |
| 4b | Respiratory failure | Forced vital capacity <30% predicted Maximal inspiratory pressure <40 cm H2O Daytime partial pressure CO2 >45 mm Hg | Prolonged daytime NIV Tracheostomy |
Control of inspiratory time (Ti) is essential in any NIV mode and assisted airway clearance with breath stacking in the volume-cycled mode. The flow-interruption trigger of dedicated mouthpiece ventilation modes does not require active inhalation or inspiratory effort and therefore is useful in even the weakest individuals. Any disruption in flow at the mouthpiece will initiate a full tidal volume breath in volume-cycled mode. A respiratory rate is usually not set, giving the user control over breath timing. In a nondedicated mode, MPV can still be utilized with assist control mode, with a back-up respiratory rate and an active circuit.31,32 Several types of mouthpieces are available, and these can be mounted on a flexible arm attached to a motorized wheelchair if the user has limited upper extremity mobility/strength. If MPV is not tolerated either because of high leak with poor mouth seal or other dysynchrony, a strategy of rotating masks between day use and night use with different facial pressure points (eg, oronasal or nasal alternating with nasal pillows) can be utilized.

Despite benefits to survival and quality of life, many with ALS do not use NIV. A recent study showed that in persons with ALS with any FVC percentage of predicted, only approximately one-third were using NIV. In addition, in those with ALS with FVC less than 50% of predicted, only 52.5% were using NIV.33

**Stage 4: Day and Night NIV**

With progressive respiratory muscle weakness, the addition of midday NIV, sometimes referred to as a “PAP (positive airway pressure) nap,” provides rest for respiratory muscles near the midpoint of the day. Once a person needs more than 16 hours of NIV, consideration should be given to the addition of mouthpiece ventilation. Mouthpiece ventilation (MPV), unlike the mask interface, allows eating and drinking, facilitates speech with breath stacking, and reduces the incidence of facial skin breakdown by reducing time spent with a mask interface. Although MPV can be used with either pressure-cycled or volume-cycled modes of ventilation, it is most commonly used in a volume-cycled mode. MPV can also function for caregiver-independent lung volume recruitment and assisted airway clearance with breath stacking in the volume-cycled mode. The flow-interruption trigger of dedicated mouthpiece ventilation modes does not require active inhalation or inspiratory effort and therefore is useful in even the weakest individuals. Any disruption in flow at the mouthpiece will initiate a full tidal volume breath in volume-cycled mode. A respiratory rate is usually not set, giving the user control over breath timing. In a nondedicated mode, MPV can still be utilized with assist control mode, with a back-up respiratory rate and an active circuit.31,32 Several types of mouthpieces are available, and these can be mounted on a flexible arm attached to a motorized wheelchair if the user has limited upper extremity mobility/strength. If MPV is not tolerated either because of high leak with poor mouth seal or other dysynchrony, a strategy of rotating masks between day use and night use with different facial pressure points (eg, oronasal or nasal alternating with nasal pillows) can be utilized.

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**Stage 4: IMV**

Because of the improvements in quality of life and survival achieved with NIV, only a very small proportion of people with progressive NMD will elect to have a tracheostomy and IMV. Those undergoing tracheostomy in the setting of acute or chronic respiratory failure should be offered the opportunity to liberate from IMV to NIV, regardless of the severity of their respiratory muscle weakness.34 For those with tracheostomy and IMV, there is a clear survival benefit on the order of years,35,36 although there are conflicting data on whether there is any significant objective improvement in quality of life.37 People using IMV continue needing airway clearance and cough augmentation after tracheostomy, and both patient and family must be made aware of the significant increase in caregiver responsibilities with this mode of mechanical ventilation before proceeding.

**Diaphragmatic Reinnervation**

Diaphragmatic pacing, which is the application of electrical stimulation to the phrenic nerves, has been used in select individuals with chronic respiratory failure. This is a reason-

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**Table 2: Guideline Criteria for Initiating Noninvasive Ventilatory Support (NIV)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Hypoventilation present with ≥1 of the following</td>
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<tr>
<td></td>
<td>Forced vital capacity (FVC) &lt;30% predicted</td>
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<td></td>
<td>Apnea-hypoxia index &gt; 10/hour</td>
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<td></td>
<td>End tidal CO₂ &gt;45 mm Hg</td>
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<tr>
<td></td>
<td>Baseline nocturnal oxygen saturation (SpO₂) &lt;95% when awake</td>
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<tr>
<td>American Thoracic Society</td>
<td>Hypoventilation signs and symptoms with ≥1 of the following</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>FVC &lt;50% of predicted (AAN, ACCP)</td>
</tr>
<tr>
<td></td>
<td>FVC &lt;80% of predicted (EFNS)</td>
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<tr>
<td></td>
<td>Maximal inspiratory pressure &lt;60 cm H₂O</td>
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<tr>
<td></td>
<td>Nocturnal SpO₂ &lt; 88% for &gt;5 minutes</td>
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<tr>
<td></td>
<td>Daytime CO₂ partial pressure &gt;45 mm Hg</td>
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<tr>
<td>American Academy of Neurology (AAN) or European Federation of Neurological Societies (EFNS), and American College of Chest Physicians (ACCP) in neuromuscular disorders</td>
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able option for those who have an intact respiratory neurostimulators to care for these complex patients is essential, along with the assessment of the respiratory muscle strength and alveolar hyperventilation at regular intervals. Defining the progressive respiratory muscle weakness and loss of function into disease stages allows for evidence-based practice guidelines for the implementation of RAD. Despite these advances, many with NMD are not using ventilatory support devices and this remains an area of opportunity to improve our delivery of care and standardize use of RADs to improve survival and quality of life for all persons with neuromuscular respiratory failure.

**Conclusion**

Persons with NMD are surviving longer due to the advancing technologies of NIV and airway clearance. A multidisciplinary team including respiratory therapists and pulmonologists to care for these complex patients is essential, along with the assessment of the respiratory muscle strength and alveolar hyperventilation at regular intervals. Defining the progressive respiratory muscle weakness and loss of function into disease stages allows for evidence-based practice guidelines for the implementation of RAD. Despite these advances, many with NMD are not using ventilatory support devices and this remains an area of opportunity to improve our delivery of care and standardize use of RADs to improve survival and quality of life for all persons with neuromuscular respiratory failure.


