CHEST

Respiratory Management of Patients With Neuromuscular Weakness

An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report

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Endorsed by the American Academy of Sleep Medicine, the American Association for Respiratory Care, the American Thoracic Society, and the Canadian Thoracic Society

BACKGROUND: Respiratory failure is a significant concern in neuromuscular diseases (NMDs). This CHEST guideline examines the literature on the respiratory management of patients with NMD to provide evidence-based recommendations.

STUDY DESIGN AND METHODS: An expert panel conducted a systematic review addressing the respiratory management of NMD and applied the Grading of Recommendations, Assessment, Development, and Evaluations approach for assessing the certainty of the evidence and formulating and grading recommendations. A modified Delphi technique was used to reach a consensus on the recommendations.

RESULTS: Based on 128 studies, the panel generated 15 graded recommendations, one good practice statement, and one consensus-based statement.

INTERPRETATION: Evidence of best practices for respiratory management in NMD is limited and is based primarily on observational data in amyotrophic lateral sclerosis. The panel found that pulmonary function testing every 6 months may be beneficial and may be used to initiate noninvasive ventilation (NIV) when clinically indicated. An individualized approach to NIV settings may benefit patients with chronic respiratory failure and sleep-disordered breathing related to NMD. When resources allow, polysomnography or overnight oximetry can help to guide the initiation of NIV. The panel provided guidelines for mouthpiece ventilation, transition to home mechanical ventilation, salivary secretion management, and airway clearance therapies. The guideline panel emphasizes that NMD pathologic characteristics represent a diverse group of disorders with differing rates of decline in lung function. The clinician's role is to add evaluation at the bedside to shared decision-making with patients and families, including respect for patient preferences and treatment goals, considerations of quality of life, and appropriate use of available resources in decision-making.

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KEY WORDS: airway clearance therapies; clinical practice guidelines; neuromuscular diseases; noninvasive ventilation; pulmonary function testing; respiratory failure; sleep-disordered breathing

ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; BT = botulinum toxin; COI = conflict of interest; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; HFCWO = high-frequency chest wall oscillation; LVR = lung volume recruitment; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; MI-E = mechanical insufflation-exsufflation; MPV = mouthpiece ventilation; MV = mechanical ventilation; NIV = noninvasive ventilation; NMD = neuromuscular disease; ONO = overnight oximetry; PCF = peak cough flow; PFT = pulmonary function testing; PICO = population, intervention, comparator, and outcome; RT = radiation therapy; SNIP = sniff nasal inspiratory pressure

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Summary of Recommendations and Suggestions

Use and Timing of Pulmonary Function Testing

1. For patients with neuromuscular disease (NMD) at risk of respiratory complications, we recommend pulmonary function testing (PFT) to assist with management decisions (Good Practice Statement).

Remarks: PFT is a low-cost intervention. The panel recommends that spirometry with forced or slow vital capacity (FVC or SVC) and maximum inspiratory and expiratory pressure (MIP/MEP) or sniff nasal inspiratory pressure (SNIP) and peak cough flow (PCF) be considered in patients with NMD when available according to regional practice patterns.

2. For patients with NMD at risk of respiratory failure, we suggest PFT at a minimum of every 6 months as appropriate to the course of the specific NMD (Conditional Recommendation, Ungraded Consensus-Based Statement).

Remarks: When performing spirometry, the panel suggests one or more of the following: vital capacity FVC or SVC, MIP or MEP, SNIP, and PCF at least every 6 months, according to regional practice patterns and availability. Clinicians should adjust the testing frequency based on the progression rate of individual NMD.

Screening for Respiratory Failure and Sleep-Related Breathing Disorders

3. For symptomatic patients with NMD who have normal PFT and overnight oximetry (ONO) findings, we suggest that clinicians consider polysomnography to assess whether noninvasive ventilation (NIV) is clinically indicated (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: A polysomnography can be used to assess whether NIV is indicated in symptomatic patients with normal PFT and ONO findings. This may require an appropriate testing facility in the community, preferably with Americans with Disabilities Act access, NMD protocols, equipment for NMD, and space for bedside caregivers. Clinical indications may vary based on the patient's age and disease progression. Polysomnography may be the preferred option for pediatric patients.

Use of NIV

4. For patients with NMD and chronic respiratory failure, we recommend using NIV for treatment (Strong Recommendation, Very Low Certainty of Evidence).

Remarks: The clinical indications for NIV can vary depending on NMD, patient age, and rate of disease progression. Any fall in FVC to $< 80\%$ of predicted with symptoms or FVC to $< 50\%$ of predicted without symptoms or SNIP /MIP to < -40 cm H_2O or hypercapnia would support the initiation of NIV or further testing as clinically indicated for individual NMD. See the text and e-Appendix 4 for more details.

5. For patients with NMD and sleep-related breathing disorders, we suggest using NIV for treatment (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: The panel suggests using the American Academy of Sleep Medicine criteria for sleep-disordered breathing and hypoventilation for adult patients and the European Respiratory Society criteria for pediatric patients.

Respiratory Parameters for Initiation of NIV

6. For patients with NMD, we suggest the use of diagnostic tests such as FVC, MIP/MEP, ONO, or evidence of sleep-disordered breathing or hypoventilation on polysomnography to predict the timing of NIV initiation (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Polysomnography is not necessary for adult patients to initiate NIV, and PFT criteria alone may be adequate. See the comments for recommendations 4 and 5.

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7. For patients with NMD requiring NIV, we suggest individualizing NIV treatment to achieve ventilation goals (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: NIV can be optimized by adjusting parameters such as mode of ventilation, inspiratory time, and inspiratory and expiratory pressures. There is no strong evidence supports one mode of ventilation over another, although a backup respiratory rate may lead to better patient-ventilator synchrony and improved gas exchange. Patients with bulbar impairment may not be able to tolerate NIV or achieve adequate ventilation. The panel suggests an ongoing assessment of sleep quality, digital downloads, leaks, oximetry (capnography where available), and determining optimal settings along with optimizing secretion management.

8. For patients with NMD and preserved bulbar function using NIV, we suggest mouthpiece ventilation (MPV) for daytime ventilatory support as an adjunct to nocturnal mask NIV (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Although MPV has been used in various NMDs to help delay the transition to mechanical ventilation (MV), disease-specific considerations such as the development of bulbar symptoms in certain NMDs (eg, amyotrophic lateral sclerosis [ALS]) may limit the use of this option.

Use of Mechanical Ventilation

9. For patients with NMD in whom NIV fails or who are intolerant of NIV (including extended daytime NIV use), who have worsening bulbar function, frequent aspiration, insufficient cough, episodes of chest infection despite adequate secretion management, or declining lung function, we suggest invasive home MV via tracheostomy as an alternative to NIV (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Discussions regarding the use of MV should be started early in the course of the illness and include goals of care discussion, the potential need for institutionalization, and the burden on caregivers. The panel suggests optimizing secretion management and airway clearance, using patient preference, treatment goals, quality-of-life considerations, and available resources (cost and care providers) to help make decisions.

Sialorrhea Management

10. For patients with NMD and sialorrhea, we suggest a therapeutic trial of an anticholinergic medication as first-line therapy with continued use only if benefits are perceived to outweigh potential side effects (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: The panel suggests an initial trial of an inexpensive oral anticholinergic medication. Clinicians can also consider more expensive but potentially longer-acting anticholinergic patch medication as the first- or second-line therapy for sialorrhea.

11. For patients with NMD and sialorrhea who have an inadequate response or are intolerant of the side effects of anticholinergic therapy, we suggest botulinum toxin (BT) therapy to salivary glands (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: See individual studies for doses of BT. It is unclear whether clinicians should consider BT or radiation therapy (RT) first and can base their decision on local expertise.

12. For patients with NMD and sialorrhea who have an inadequate response or are intolerant of the side effects of anticholinergic therapy, we suggest salivary gland RT (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Data on RT are limited. See individual studies for doses. It is unclear whether clinicians should consider BT or RT first and can base their decision on local expertise.

Airway Clearance Therapies

13. We suggest clinicians consider glossopharyngeal breathing for lung volume recruitment (LVR) and airway clearance for patients with NMD and hypoventilation (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: LVR is low cost and can be performed by the patient independently with minimal assistance and training.

14. For patients with NMD and reduced cough effectiveness, we suggest manually assisted cough techniques independently or added to other modalities such as LVR (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Manually assisted cough techniques are low cost but require caregiver assistance and training.

15. For patients with NMD and reduced lung function or cough effectiveness, we suggest regular use of LVR (breath stacking) using a handheld resuscitation bag or mouthpiece (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: LVR with a handheld device or mouthpiece is low cost but requires caregiver assistance and training. Manually assisted cough is more effective when added to volume recruitment or the expiratory phase of mechanical cough assist.

16. For patients with NMD and reduced cough effectiveness, which cannot be adequately improved with alternative techniques, we suggest the addition of regular mechanical insufflation-exsufflation (MI-E; cough assist device) (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Implementing the recommendation requires caregiver assistance and training and a MI-E device (cough assist device), which can increase costs and should be considered based on local resources.

17. For patients with NMD and difficulties with secretion clearance, we suggest using high-frequency chest wall oscillation (HFCWO) for secretion mobilization. In addition, we suggest that HFCWO be combined with airway clearance therapies such as cough assistance or LVR (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Implementing the recommendation requires caregiver assistance and training and an HFCWO device, which can increase costs and should be considered based on local resources and shared decision-making.

Background

Respiratory failure is a common complication in patients with NMD.[1] Respiratory muscle weakness in patients with NMD can lead to inadequate ventilation, hypoventilation at night, and the inability to mobilize secretions that frequently are the cause of death in this population.[2,3] Sleep-related breathing disorders are common initial symptoms of NMD.[4] Data on the treatment of respiratory failure in NMD are limited. NMDs present at different ages and progress at variable rates, making it difficult to provide a single set of guidelines. A Cochrane review found no studies that compared invasive and noninvasive MV or intermittent positive pressure vs negative pressure ventilation.[5] Guidance on this topic from professional societies is limited.[2,6-17] The Swiss and French societies have proposed recent guidelines; however, they have limited application in the United States because of the lack of respiratory therapist support in the United States and the national coverage determination for using in-home MV with a different standard of care.[16-18]

Patients with NMD often are cared for by interprofessional teams consisting of pulmonologists, neurologists, respiratory therapists, physical and occupational therapists, pediatricians, internists, and family physicians. This document aims to guide providers involved in the respiratory care of patients with NMD with the understanding that variations in the patterns of respiratory muscle involvement and timing of clinical presentation and progression of NMDs occur that require an understanding of the patient's underlying disease process before using the recommendations.

Study Design and Methods

Expert Panel Composition

The chair of the panel (A. K.) was reviewed for potential conflicts of interest (COIs) and was approved by the CHEST Professional Standards Committee. The chair nominated additional panelists based on their expertise in potential guideline questions, which the Professional Standards Committee approved after reviewing their COI disclosures. The panel includes adult and pediatric pulmonologists, critical care specialists, sleep medicine specialists, a respiratory therapist, a methodologist, and a patient representative. COIs are listed in e-Appendix 1.

Panelists were required to disclose any potential financial or intellectual COIs throughout guideline development. Panelists found to have no substantial COIs were approved, whereas nominees with potential intellectual or financial COIs that were manageable were approved with management. Panelists approved with management were prohibited from voting on recommendations in which they had substantial COI. A grid was created to track COIs for each clinical question and was used during discussion and voting to ensure transparency and observation of the management terms (e-Appendix 1). A panelist submitted a late COI disclosure related to a relationship with a company with a premarket product in the area addressed by this guideline. The relationship occurred during the development, but was not disclosed a priori for review by the Professional Standards Committee as required by CHEST policy. When reporting the relationship, a post hoc review determined that prior work with unrelated products and the existence of the relationship did not influence or alter the final recommendations.

Question Development and Systematic Literature Searches

The panel drafted nine clinical questions using the population, intervention, comparator, and outcome (PICO) format (Table 1). These questions were selected based on the approved scope of the guidelines. Based on PICO questions, database-specific search strategies were developed using a combination of medical subject headings and key words from the National Library of Medicine. MEDLINE via PubMed and the Cochrane Library was searched initially in November 2018.

TABLE 1] Structured Clinical Questions

Topic	Population	Intervention(s)	Comparator(s)	Outcomes	Study Designs
Use of PFT	Patients with NMD (age > 6 y) at risk of respiratory failure	PFT and measurement of lung function parameters	No PFT or measurement of lung function parameters	Disease progression, SDB, patient preference, clinical use	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
Timing of PFT	Patients with NMD (age > 6 y)	Respiratory insufficiency testing at least every 6 mo	Respiratory insufficiency testing 1/y	Disease progression, patient preference, clinical use	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
Testing for SDB	Patients with NMD (age > 6 y)	Testing for SDB	No testing for SDB	QoL, symptom improvement, survival, patient preference, clinical use, sleep architecture	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
Use of NIV	Patients with NMD (age > 6 y) and respiratory failure	NIV	No NIV	Survival, disease progression, QoL, symptom improvement, patient and caregiver preference, clinical use, adverse events	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
Respiratory parameters for initiation of NIV	Patients with NMD (age > 6 y)	Use of respiratory parameters to initiate NIV	No consideration of specific respiratory parameters to initiate NIV	Survival, symptom improvement, patient preference, clinical use	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
NIV ventilation strategies	Patients with NMD (age > 6 y) using NIV	(Comparative effectiveness) of the following noninvasive ventilator strategies; bilevel pressure-targeted (S mode), backup rate (S/T, PC, PAC mode), volume targeted, VAPS, negative pressure ventilation		Survival, symptom improvement, QoL, patient preference, sleep architecture, adverse events	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
MPV	Patients with NMD (age > 6 y) using NIV	MPV	Other NIV methods (facemask, helmet, and so on)	Survival, symptom improvement, QoL, patient preference, adverse events	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
Invasive ventilation	Patients with NMD (age > 6 y) and respiratory failure	Invasive home ventilator therapies through tracheostomy	No invasive home ventilator therapies, palliation, continuous NIV	Survival, symptom improvement, QoL, patient preference, adverse events	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)
Airway clearance techniques	Patients with NMD (age > 6 y)	Selected airway clearance therapies	No airway clearance therapy	Secretion management, survival, symptom improvement, QoL, patient preference, clinical use, adverse events	Cohort, case-control RCTs, systematic review, meta-analyses; excluded: case reports and case series (n < 11)

MPV = mouthpiece ventilation; NIV = noninvasive ventilation; NMD = neuromuscular disease; PAC = pressure assisted control; PC = pressure; PFT = pulmonary function testing; QoL = quality of life; RCT = randomized controlled trial; SDB = sleep-disordered breathing; S/T = spontaneous/timed; VAPS = volume-assured pressure support.

TABLE 2] Certainty of Evidence

Certainty of the Evidence	Level of Confidence in the Estimate of the Effect[22]
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but a possibility exists that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The study selection process is detailed in e-Appendix 2. Based on searches for the nine PICO questions, 6,761 records were screened, from which 108 unique studies were included in the analysis. A comprehensive search update was conducted in September 2020. Seven hundred thirty-five records were screened, from which 18 additional studies were included in the synthesis. In July 2021, a further search update was conducted to incorporate evidence on the use of anticholinergics. One hundred sixty-three records were screened, and two studies were included. The searches were restricted to English-language publications, but were not limited by study design or publication date. Reference lists of relevant identified studies also were reviewed, and panelists conducted ongoing surveillance of the literature.

Study Selection and Data Abstraction

Literature search results were reviewed for relevance over two rounds of study selection that followed a standard process of independent, duplicate work with disagreement resolution via discussion. The panelists screened identified studies using predefined inclusion and exclusion criteria based on the PICO components of the clinical questions and the study design (Table 1, e-Appendixes 2, 3). Screening forms were created using the web-based systematic review software DistillerSR (Evidence Partners), and the software was used to facilitate the selection process. This process initially was applied to the title and abstract screening, then to full-text screening (e-Appendixes 2, 3). The aim of this process was to identify all studies meeting the inclusion criteria.

Structured data tables were used to abstract data on study characteristics and outcomes. The methodologist independently performed data abstraction, and a second panelist independently reviewed the abstracted data. Discrepancies were resolved by discussion.

Risk of Bias Assessment

The methodologist assessed the risk of bias in all included studies using DistillerSR. DistillerSR assessment forms were selected, as appropriate, based on the study design. The forms were adapted from version 2 of the Cochrane risk-of-bias tool for randomized trials, the CLARITY Group at McMaster University's Tool to Assess Risk of Bias in Cohort Studies, the CLARITY Group at McMaster University's Tool to Assess Risk of Bias in Case-Control Studies, and the Documentation and Appraisal Review Tool for systematic reviews.[19-21]

Data Analysis

The limited available homogeneous evidence precluded the pooling of data from individual studies and meta-analyses. The textual description of the effects reported in the studies was provided by the outcome of interest for each PICO question. Study findings were presented in evidence tables to compare results from each included study reporting on the outcome of interest.

Assessing the Certainty of the Evidence

The certainty of the evidence was assessed for each outcome of interest using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[22,23] This approach categorizes certainty as high, moderate, low, or very low, reflecting the extent to which panelists are confident in the findings to support a recommendation (Table 2).[22,23] Evidence profiles, including a summary of the results and the certainty of evidence assessment, were created using the GRADEPro Guideline Development Tool.[24]

Recommendation Drafting

The panel used the evidence profiles to create evidence-to-decision frameworks for each PICO question.[25] Using the evidence-to-decision frameworks, panelists drafted recommendations that were graded using the CHEST grading system based on the GRADE approach (Table 3).[26] In instances of insufficient evidence where guidance was still warranted, a conditional suggestion was developed, and "Ungraded Consensus-Based Statement" replaced the grade.[27]

Consensus Development

All drafted recommendations were presented to the panel in an anonymous online voting survey. Panelists without a relevant COI voted on each recommendation to achieve consensus using a modified Delphi technique.[27] Panelists also had the option to provide open-ended feedback on each statement. Each guidance statement required a 75% voting participation rate and at least 80% consensus for approval and inclusion in the guidelines. Based on the feedback provided, the panel revised any recommendation that did not meet these criteria and distributed and completed a new voting survey that included suggested changes for up to three rounds. After three rounds, all recommendations reached consensus.

Results

Use and Timing of PFT

Evidence and Evidence-to-Decision: To evaluate the usefulness of PFT in NMD, the panel reviewed 1,561 abstracts and selected 22 studies for review (e-Tables 1a-1c).[28-49] All evidence was determined to be indirect because it assessed the predictive value of PFT to assess survival, respiratory events, and sleep-disordered breathing, which differed from the research question focused on the usefulness of PFT to predict disease progression. The identified evidence was used to develop a good practice statement. The desirable effects were determined to be large, because evidence and standard

TABLE 3] CHEST Grading System

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We are very confident that the true effect lies close to that of the estimate of the effect.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but a possibility exists that it is substantially different.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Strong recommendation, very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, high-quality evidence	Benefits closely balanced with risks and burden.	We are very confident that the true effect lies close to that of the estimate of the effect.	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak (conditional) recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden.	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but a possibility exists that it is substantially different.	Best action may differ depending on circumstances or patients' or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak (conditional) recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Good practice statement	Benefits clearly outweigh risk and burdens, or vice versa.	Based on indirect evidence or inference from already commonly accepted as beneficial practice.	Action is viewed as obviously beneficial or standard of care; it is unlikely that direct research will be conducted.

(Continued)

TABLE 3] (Continued)

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Ungraded consensus-based suggestions			
Ungraded consensus-based statement	Uncertainty because of lack of evidence, but expert opinion that benefits outweigh risk and burdens or vice versa.	Insufficient evidence for a graded recommendation.	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate.

clinical practice suggest that PFT is a common diagnostic method to assess the progression of respiratory failure and predictors of survival in patients with NMD (e-Appendix 4). No clear harms were identified, and undesirable effects were determined to be trivial. The balance of effects strongly favors the intervention and supports its use as standard clinical practice.

Among the PFT parameters identified as predictors of clinical outcomes, the panel recommends the measurement of vital capacity (FVC or SVC), MIP or MEP, SNIP, or PCF in patients with NMD. A review of 142 abstracts did not identify any studies that addressed the impact of the frequency of PFTs on disease progression, quality of life, or clinical use in NMD. Based on expert opinion, the panel believed that testing and follow-up at least every 6 months have benefits over yearly or as-needed testing. In addition, the panel did not identify any harm from the timing of testing, so the balance of desirable and undesirable effects favors earlier testing. Using a consensus-based approach, the panel chose an interval of 6 months, acknowledging that although the rate of progression of each NMD is different, in some NMDs, such as ALS, patients may show a significant change in respiratory parameters in 3 to 6 months, whereas in stable or slowly progressing diseases such as Duchenne muscular dystrophy, PFT could be performed at less frequent intervals such as every 12 months.

Additional Comments and Implementation Recommendations: PFT is a low-cost intervention that can be performed in the office or with home-based monitoring.[50] Spirometry should be performed with a mouthpiece and a nasal clip or a mask (if the patient cannot close their mouth). The following values are considered abnormal: FVC $<$ 80% predicted, MIP $<$ –60 cm H_2O, MIP $<$ 40 cm H_2O, and PCF $<$ 270 L/min in individuals $\geq$ 12 years of age (Fig 1).[10,51-53] SNIP can be substituted for MIP in case of significant NMD.[10,51-53] The panel found limited data on PFT in the supine vs erect postures because studies were based on retrospective data with small sample sizes.[29,45,48,54-56] Access to supine testing also is limited by the use of body boxes for testing in the United States. Although the panel did not make a recommendation in this area, we do not limit or advise against the use of supine testing when available. Similarly, although the panel recommended testing every 6 months, more frequent testing may be performed based on patient symptoms.

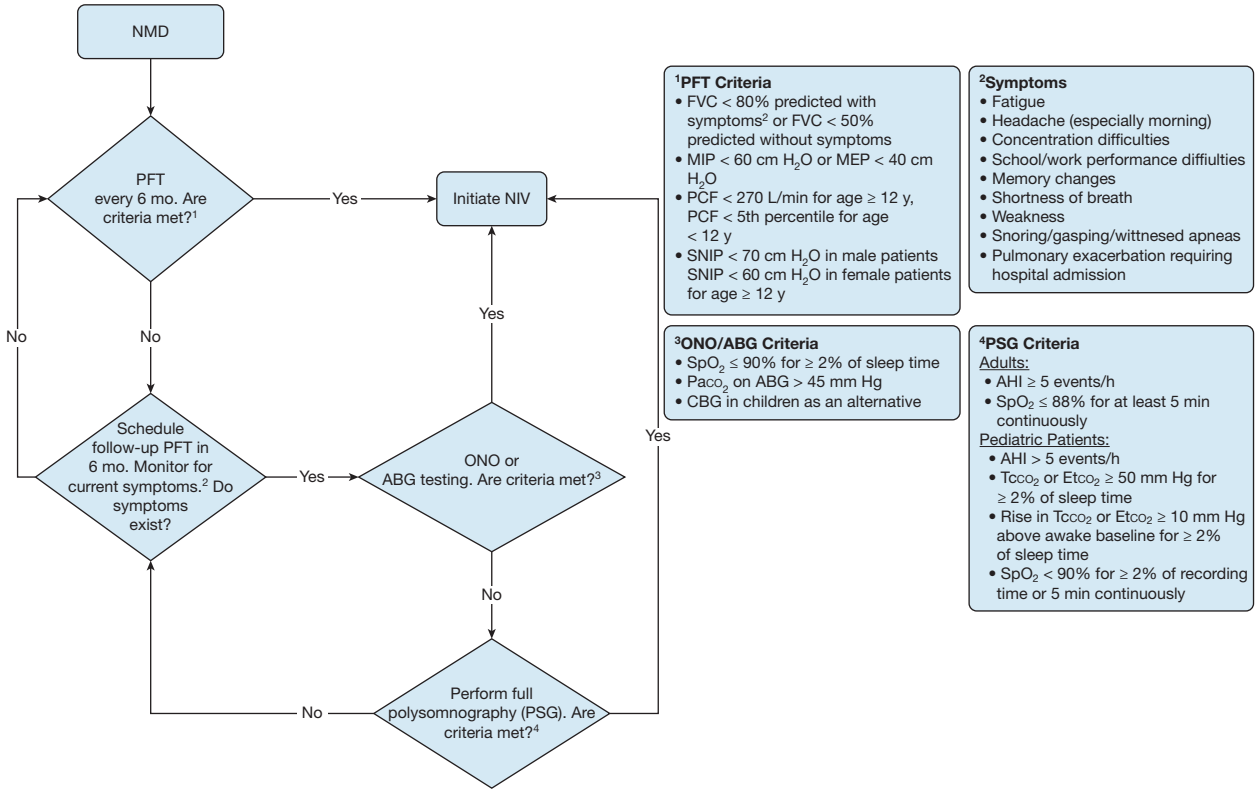

Figure 1 – *Flowchart for NIV initiation for patients with NMD showing respiratory failure symptoms. ABG = arterial blood gas; CBG = capillary blood gas analysis; $ETCO_2$ = end-tidal CO_2; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; NIV = noninvasive ventilation; NMD = neuromuscular disease; ONO = overnight oximetry; PCF = peak cough flow; PFT = pulmonary function testing; SNIP = sniff nasal inspiratory pressure; SpO_2 = arterial oxygen saturation; $tcPCO_2$ = transcutaneous PCO_2.*

Certain populations, such as patients with bulbar dysfunction, may not be able to perform PFT. Daytime PFT also can be a good measure of sleep-related hypoventilation and can correlate with time spent with oxygen saturation of ≤ 90% and PCO_2 of ≥ 45 mm Hg on arterial blood gas.[30,33] More frequent testing may be possible with the help of trained caregivers and home-based monitoring.[50] The frequency of respiratory testing and the role of spirometry in the supine vs erect postures are important areas of future research. Home testing may allow for more frequent tests at shorter intervals and may help to determine the optimal interval for testing for various NMD disorders, especially those with faster progression.

Screening for Respiratory Failure and Sleep-Related Breathing Disorders

Evidence and Evidence-to-Decision

The panel reviewed 2,192 abstracts and selected five studies for review (e-Table 2).[57-61] Observational studies of the three types of sleep testing—ONO, traditional type I in-laboratory polysomnography, and home sleep testing—suggest moderate desirable effects as a result of identifying sleep-disordered breathing and minimal undesirable effects with no indication of harm (e-Appendix 4). No data were available on the frequency or timing of polysomnography, ONO, or home sleep testing with respect to NMD diagnoses, with a consensus recommendation to consider sleep history and symptoms to determine the need for testing (Fig 1). The balance of risk and benefits was considered to favor the intervention, with very low certainty of evidence. Based on very limited evidence, transcutaneous and end-tidal CO_2 may be helpful in detecting hypoventilation and initiating and managing NIV.[39,62-64] Home-based overnight capnography is feasible and has been used as one of the criteria to initiate respiratory support.[39,64]

Polysomnography is not necessary for adult patients to manage NMD if PFT or ONO criteria support using NIV (Fig 1).[65] Sleep testing can be helpful when concern exists that PFT and clinical evaluation are not capturing complications such as hypoventilation.[13,39,57-60,65-67] Full polysomnography is suggested at least once in pediatric patients and adults with symptoms such as daytime tiredness, fatigue, excessive daytime sleepiness, history of

snoring, apneic episodes, or pauses in breathing.[13,65] Nocturnal ONO and capnography can detect early signs of nocturnal hypoventilation in some adult NMD populations.[66] ONO also has the advantages of low cost and easy repeatability. ONO can be used to assess nocturnal desaturation to < 88% for 5 min, which may qualify patients with NMD for NIV in the absence of OSA, and for monitoring the adequacy of NIV support to ensure that oxygen saturations are > 90% for > 90% of the recording on NIV.

Additional Comments and Implementation Recommendations

The use of polysomnography in patients with NMD depends on the availability of sleep laboratories, preferably with access compliant with the Americans with Disabilities Act of 1990, trained staff, and protocols to address hypoventilation and OSA. The limited availability of such laboratories likely will impact provider decisions to use polysomnography significantly. ONO or PFT could be used as an alternative to polysomnography and can be considered more frequently, for example, every 6 months or as indicated, to help with NIV decisions.[66] Hypoventilation is difficult to detect during polysomnography.[13-15,68,69] Patients with NMD are at risk of respiratory complications related to hypoventilation, which often manifest during sleep, especially rapid eye movement sleep.[60,67,70]

The panel recommends using the AASM guidelines for scoring hypoventilation in adults[15] and the ERS guidelines for pediatric patients because these define pediatric hypoventilation, specifically in those with NMD.[13] In children and adults, the surrogates of arterial P_{CO_2} are end-tidal P_{CO_2}, which can be affected by mask leak during titration or transcutaneous P_{CO_2}. Capillary blood gas may be used in children instead of arterial blood gas. Hypoventilation is scored in adults on polysomnography when the arterial P_{CO_2} (or surrogate) is ≥ 55 mm Hg for ≥ 10 min or an increase in the arterial P_{CO_2} (or surrogate) of ≥ 10 mm Hg occurs (in comparison with an awake supine value) to a value exceeding 50 mm Hg for ≥ 10 min.[15] For pediatric patients, hypoventilation is scored when the arterial P_{CO_2} (or surrogate) is ≥ 50 mm Hg for ≥ 2% of total sleep time or peripheral capillary oxygen saturation is ≤ 90% for 2% of the recording time.[13,14] The value of testing to identify sleep-disordered breathing and hypoventilation may vary across specific NMDs and may impact patient decisions. For example, pediatric patients and patients with NMD associated with cardiomyopathies are more likely to benefit from this diagnostic intervention.[39,64]

Use of NIV

Evidence and Evidence-to-Decision

The panel reviewed 763 abstracts and selected 25 studies for review (e-Tables 3a-3e).[71-95] The intervention was the use of NIV, and the comparator was no NIV. Outcomes included survival, respiratory function, sleep, cognitive function, and quality of life (e-Appendix 4). The desirable effects of NIV were moderate, and the undesirable effects were small, with a no clear harm, with a net benefit that favors NIV. Given the life-threatening nature of chronic respiratory failure, despite the low certainty of the evidence, the panel made a strong recommendation for the use of NIV based on the GRADE guidelines.[23] In the opinion of the panel, no important uncertainty or variability was likely in how patients value these results, such as improved survival. Studies on sleep quality and respiratory parameters during sleep were observational, with no direct comparisons between NIV and CPAP. The panel provided a conditional recommendation for using NIV for sleep-related breathing disorders. Although no cost-effectiveness study was conducted for chronic respiratory failure or sleep-related breathing disorders, the panel believed that the net benefit justified the resources to initiate NIV.

Additional Comments and Implementation Recommendations

The evidence was predominantly from older children (≥ 12 years) and adults with NMD, with most studies in adults with ALS, although patients with Duchenne muscular dystrophy also are included.[71-96] Uncertainty exists regarding to what extent the evidence applies to younger children with NMD. The panel anticipates that NIV is feasible to implement in many patients. However, some patients will decline, and the panel recommends shared decision-making with patients and caregivers.

Respiratory Parameters for Initiation of NIV

Evidence and Evidence-to-Decision

The panel reviewed 422 abstracts and selected five studies for review.[97-101] The respiratory parameters considered included the apnea-hypopnea index, hypoventilation indexes such as time spent with oxygen saturation < 90% during the night, end-tidal P_{CO_2} or

transcutaneous CO_2, FVC, MIP, MEP, PCF, and SNIP (e-Appendix 4). Outcomes included timing of NIV, care use, patient preference, symptom improvement, and mortality (e-Table 4). The desirable effects of NIV were moderate, and the undesirable effects were small, with no clear harm, with the net benefit favoring NIV. The certainty of the evidence was very low. This recommendation places a higher value on the potential for improvement of outcomes that are important to patients, including survival and symptom (Fig 1) mitigation, and a lower value on the potential risks and inconveniences of NIV. Given the significant impact of respiratory failure on morbidity and mortality, the testing and timing of NIV were considered a priority.

Additional Comments and Implementation Recommendations

Evidence was generated predominantly from adults with ALS, because it is the most common NMD.[102] It must be applied judiciously to younger children, adolescents, and adults with non-ALS diagnoses. The panel recommends considering positive airway pressure or NIV, as appropriate, in symptomatic patients with FVC of $<$ 80% of normal; those with FVC of $<$ 50% predicted or impairment of other parameters such as MIP of $<$ –60 cm H_2O, MEP of $<$ 40 cm H_2O, or PCF of $<$ 270 L/min; or based on the polysomnography results if polysomnography was indicated or the presence of hypercapnia (awake $Paco_2$ $>$ 45 mm Hg).[10,51,52] The panel recommends continuing to follow up patients with serial PFT on a 6-month basis and offering NIV when indicated. The panel did not distinguish between the presence or absence of bulbar symptoms when offering NIV and recommends respecting patient and family preferences and quality-of-life considerations.

NIV Strategies

Evidence and Evidence-to-Decision

The panel reviewed 1,383 abstracts and selected five studies for review (e-Tables 5a-5e).[103-107] No strong evidence was found to support one method of NIV ventilation over another. However, a backup respiratory rate achieved better patient-ventilator synchrony and improved gas exchange (e-Appendix 4). No clear harms were identified for specific ventilator strategies, except those related to inappropriate settings based on patient characteristics or inherent to NIV (mask) use. The overall certainty of the evidence was very low.

Additional Comments and Implementation Recommendations

The recommendation emphasizes the need to individualize NIV treatment. The optimal method of NIV for each patient can be determined only by a careful ongoing assessment of patient comfort, sleep quality, digital downloads, unintentional leaks, oximetry (capnography when available), and secretion management.[13,65] Certain patients with ALS with bulbar impairment may not tolerate NIV or achieve adequate ventilation.[65]

Mouthpiece Ventilation

Evidence and Evidence-to-Decision

The panel reviewed 44 abstracts and selected four studies for review (e-Table 6).[108-111] The desirable effects of MPV are unknown, but potentially include delaying or avoiding tracheostomy and improving speech, cough effectiveness, and the coordination of breathing and swallowing (e-Appendix 4). Undesirable effects were considered trivial, without identified harmful consequences with the balance of risk and benefits, probably favoring the intervention with very low certainty of the evidence.

Additional Comments and Implementation Recommendations

MPV or sip ventilation allows ventilatory support as needed through an angled mouthpiece and has been used successfully to avoid tracheostomy.[111] Progressive bulbar symptoms (eg, in ALS) may limit the use of this option. Access to MPV is not universal, which may promote health inequities. This is counterbalanced by the possible delay or avoidance of tracheostomy, reducing the burden of care.[111] Immediate availability of a handheld resuscitation bag for manual ventilation may be required for technical or ventilator failure, along with patient and caregiver training.

Use of MV

Evidence and Evidence-to-Decision

The panel reviewed 390 abstracts and selected 10 studies for review (e-Table 7).[82,112-120] Desirable effects of invasive MV at home by tracheostomy, including survival and improvement in sleep quality, were large compared with no ventilatory support and were equal to or provided a small benefit over NIV (e-Appendix 4). Undesirable effects included an increased risk of hospitalization, lower quality of life, and caregiver

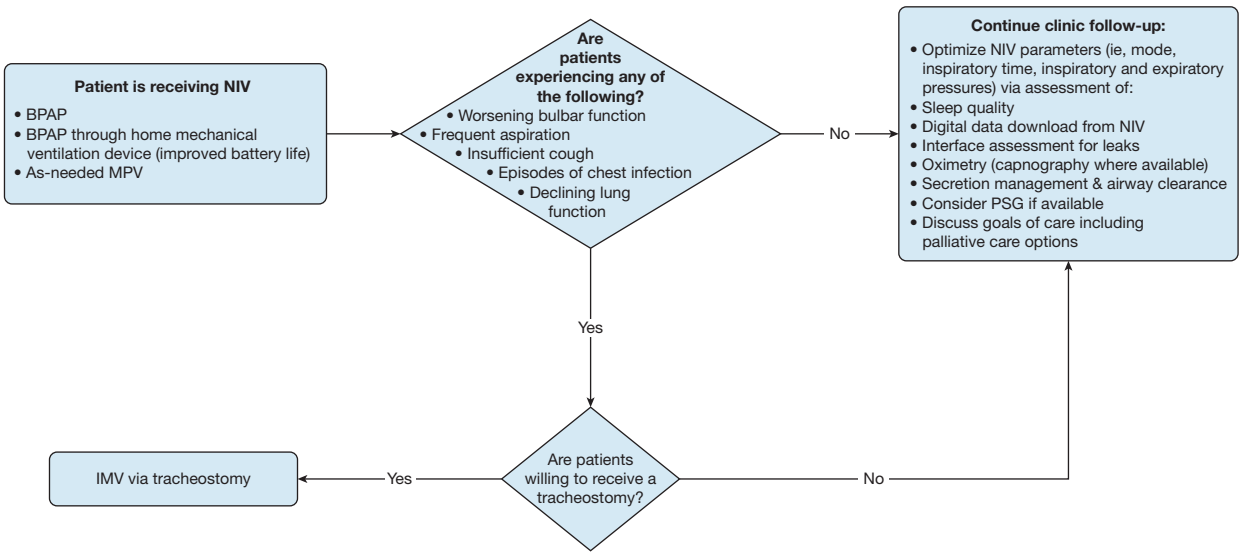

Figure 2 – *Flowchart for NIV intolerance for patients with NMD showing respiratory failure symptoms. BPAP = bilevel positive airway pressure; IMV = invasive mechanical ventilation; MPV = mouthpiece ventilation; NIV = noninvasive ventilation; NMD = neuromuscular disease; PSG = polysomnography.*

burden. Uncertainty and variability exist in how patients value outcomes, such as improved survival, compared with undesirable effects. The preponderance of evidence favors invasive home MV via tracheostomy as a treatment option for patients with progressive respiratory failure, particularly those unable to clear secretions or with changes in mental status such as frontotemporal dementia (Fig 2). However, continuous NIV also may be a possibility.[111] Both invasive ventilation and full-time NIV should be considered acceptable options based on patient preferences, tolerability, ability to maintain mouthpiece ventilation, and availability of resources.

Additional Comments and Implementation Recommendations

MV is associated with high costs and caregiver burden compared with NIV.[121,122] Most evidence comes from patients with ALS and may not be extrapolated to patients with NMD with different progression and variable degrees of bulbar involvement. Some data suggest that in slowly progressive NMD, two-thirds of patients receiving MV reported improved quality of life.[123] Other data limitations include inequalities in study groups selected for invasive home MV versus NIV, differential follow-up, and treatment decisions and allocations based on patient preference. Currently, no consensus exists on when, if desired, a patient should start invasive home MV, with recommendations ranging from 12 to 24 h for NIV based on patient comfort and preference. Many patients can manage 24-h NIV effectively, and the decision to transition to MV must not be solely time-based.[111] Also, local expertise can drive care choice between MV and NIV, such as ease of administration during sleep, oral feeding, talking, and facial expression with invasive ventilation (Fig 2).

Sialorrhea Management

Evidence and Evidence-to-Decision

Management of sialorrhea was considered a high priority in NMD. The panel reviewed 2,714 abstracts and selected 17 studies for review (e-Tables 8a-8c). Salivary secretion management included anticholinergic agents, BT therapy, and RT (Table 4). For most salivary secretion management options, the balance of risks, including treatment-specific adverse events, and benefits, such as improvement in symptoms, was considered to favor or probably to favor the intervention. Exceptions were anticholinergics, where the balance was neutral because some patients feel symptomatic relief, whereas others do not tolerate them well, and RT, where balance of benefits and risks is unclear (e-Appendix 4). Specifically, the harm may outweigh the benefits for RT in some patients. However, patients with significant debility resulting from sialorrhea can obtain achieve long-term permanent relief from this intervention. The certainty of the evidence was low to very low for all interventions.

Concern exists regarding inequities in access, given the cost of some medications and variable insurance

TABLE 4] Recommended Therapies for Sialorrhea

Therapy	Suggestions	Remarks
Anticholinergic medications	• An initial trial of an inexpensive oral anticholinergic is suggested. • Continue to use if the benefits are greater than the side effects. • More expensive and potentially longer-acting anticholinergic patch medication also can be considered.	• Relatively inexpensive and readily available. • Individual patient benefits and adverse events can be assessed easily.
Botulinum toxin therapy to salivary glands	• Limited data, doses are not defined. • See individual studies for doses in e-Table 8b.	• Inexpensive, lasting beneficial effects on salivary function. • May need to be repeated. Associated with viscous saliva and mild to moderate pain.
Salivary gland RT	• Limited data, doses not defined. • See individual studies for doses e-Table 8c.	• Long-lasting relief; however, associated with irreversible dryness. • Suggest reserving RT to experienced centers.

RT = radiation therapy.

coverage for RT. Most of the interventions were considered acceptable or probably acceptable to the stakeholders except for RT, which was considered to be of uncertain acceptability. The interventions were considered feasible to implement.

Additional Comments and Implementation Recommendations

Sialorrhea is common in NMD, particularly ALS, and can be very distressing, reducing quality of life and increasing the risk of aspiration and pneumonia because of problems with swallowing, airway protection, and cough effectiveness. Therefore, the panel recommends starting with a trial of anticholinergic agents, which are relatively inexpensive and readily available. Escalation to more expensive and more convenient anticholinergic patches or subcutaneous glycopyrrolate formulations could be considered after those initial trials. See e-Table 8a for individual doses used in clinical trials.

BT therapy is inexpensive, injections are simple and not overly uncomfortable, and the beneficial effect on salivary function can last weeks to months. However, studies are limited by observational data from a small number of patients, the risk of bias, subjective measurements, incomplete intervention description, and loss to follow-up. In addition, differences in the treatments exist (botulinum A vs B, different doses and locations, and parotid vs submandibular glands). See e-Table 8b for individual doses used in the trials. The patients considered the adverse effects mild to moderate. Because of the variability in the literature, the panel did not provide a recommended dose.

Limited data have been published on RT for sialorrhea in patients with NMD. The certainty of the evidence is limited by the unblinded observational design of these studies and the subjective improvement assessment bias. The high variability in the protocols (for example, type of energy, strength, and duration of RT), medical center experience, and degree of sialorrhea limited the comparison between studies to provide firm recommendations. The panelists recommended reserving the therapy to experienced centers. See e-Table 8c for individual doses used in the trials. Only one trial compared BT with RT and did not show significant differences in drooling between treatment methods.[124]

Airway Clearance Techniques

Evidence and Evidence-to-Decision

Impairment of cough and airway clearance because of muscle weakness, glottic dysfunction, and low lung volumes increases respiratory morbidity and mortality risk. Thus, airway clearance techniques were considered a high priority in NMD, and the panel reviewed 2,714 abstracts, selecting 36 studies for review (e-Tables 8d-8h).[125-160] Airway clearance techniques included glossopharyngeal breathing, MI-E, manually assisted cough, LVR by air stacking, and HFCWO (Table 5). These techniques involve cough augmentation to mobilize secretions and remove secretion from both proximal and peripheral airways leading to desirable effects, including improved lung function and reduced pulmonary morbidity. This is achieved by supporting the inspiratory or expiratory muscles or both. These

TABLE 5] Recommended Airway Clearance Therapies

Technique	Indications	Description	Remarks
GPB ("frog breathing")	Hypoventilation	Positive pressure breathing method using muscles of the mouth, tongue pharynx, and larynx	• Low cost • Performed by the patient independently
MAC	Reduced cough effectiveness	Abdominal thrust or lateral costal compression to generate expiratory flow.	• Low cost • Requires caregiver assistance
LVR ("breath stacking")	Reduced lung function or cough effectiveness	Handheld resuscitation bag or mouthpiece to inflate lungs to maximum inspiratory capacity without intervening expiration	• Low cost • Requires caregiver assistance
MI-E (cough assist device)	Reduced cough effectiveness not improved with alternative techniques	Alternating positive and negative pressure using a facemask or artificial airway. Effective for both upper and lower airway secretions.	• Expensive MI-E device • Requires caregiver assistance • Reduces morbidity and hospitalization, can have procedure intolerance
HFCWO combined with cough assistance or LVR	Difficulties with secretion clearance	Fit-tested vest that produces vibrations to mobilize peripheral airway secretions that then are cleared with cough or LVR to improve expiratory airflow	• Expensive HFCWO device • Requires caregiver assistance • Can have procedure intolerance

GPB = glossopharyngeal breathing; HFCWO = high-frequency chest wall oscillation; LVR = lung volume recruitment; MAC = manually assisted cough; MI-E = mechanical insufflation-exsufflation.

techniques are not mutually exclusive; a combination of therapies can help to achieve better secretion clearance.

For these airway clearance options, the balance of risks, including technique-specific adverse events and benefits, was considered to favor or probably favor the interventions. Still, the certainty of the evidence was low to very low for all interventions (e-Appendix 4). Given the certainty of the evidence, the panel recommended the use of airway clearance techniques based on local resources, expertise, and shared decision-making with patients. In the opinion of the panel, no data show superiority of one specific airway clearance technique over another, and the panel recommends making decisions on the use of individual techniques based on local resources and patient-related conditions such as intellectual disability, bulbar dysfunction, and hand dexterity in making clinical decisions. Two reviews have discussed these issues in detail.[9,12]

Concern exists regarding inequities in access, given variable insurance coverage for MI-E and HFCWO. Most of the interventions were considered acceptable or probably acceptable by stakeholders except for HFCWO, which was deemed to be of uncertain acceptability. The interventions were feasible or probably feasible except for HFCWO, for which feasibility was considered uncertain depending on availability at individual centers.

Additional Comments and Implementation Recommendations

Low-quality evidence suggests that regularly increasing lung volumes and expiratory cough flows with LVR has immediate and long-term effects on vital capacity, maximum inspiratory capacity, and assisted cough flows. Regular LVR may have a positive impact on clinical outcomes. No evidence suggests that one method of LVR is superior to another, for example, resuscitation bag vs MPV,[157] or volumetric cough mode,[132] although MPV availability improves autonomous LVR. An LVR resuscitation bag is inexpensive, and the technique is easy to learn for caregivers. Effectiveness can be limited by bulbar function and compliance with the respiratory system. More randomized controlled trials are needed to evaluate the effectiveness of LVR with objective adherence measures.

The advantages of LVR through glossopharyngeal breathing include that the technique does not require resources and has no documented adverse consequences.[161] However, not all patients can perform glossopharyngeal breathing effectively, and training is required. Manually assisted coughing, however, is readily available, can be taught in a single visit, and is feasible on its own or with an LVR maneuver.[136]

MI-E is beneficial, but may require caregiver assistance and may be less effective in patients with bulbar impairment.[162] HFCWO may be used in some cases; however, data on the use of HFCWO in patients on NIV are limited.[163] The panel recommends individualized therapy because some may find the treatment uncomfortable, like the frail and elderly or those with significant musculoskeletal deformities. MI-E and HFCWO also are associated with high costs.

Summary

Respiratory failure is common and often is the final cause of death in patients with NMD. In this article, we examined the literature on the management of respiratory failure in patients with NMD to provide evidence-based and expert guidance to clinicians. In addition, we offered recommendations where evidence allowed and consensus-based and best practice statements in areas we thought warranted comment, despite a lack of high-quality evidence.

These guidelines have several limitations. NMDs are a heterogeneous group of disorders, and it is difficult to provide a unique set of recommendations for each specific NMD. In addition, randomized controlled trials on specific NMDs are limited. Furthermore, a significant portion of the evidence is based on ALS, because data on other slowly progressive diseases are limited and elements of the guidelines may need to be individualized according to the rate of progression of an individual patient's illness (e-Appendix 3). Finally, the guideline focus on diagnosis and initiation of therapies and do not go into the details of NIV or MV, which would require separate guidelines. Despite these limitations, these guidelines provides practicing clinicians with the best possible evidence to help manage patients in clinical practice.

The guidelines panel recommends shared decision-making with patients and their families, including respect for patient preferences, treatment goals, and quality-of-life considerations. Access to these recommendations by patients and clinicians may depend on local resources and private vs public health care, and in some cases may require a referral to a specialist center. These guidelines should be an opportunity for advocacy to ensure equal access for those who meet the suggested inclusion criteria, because some recommendations can increase health inequities. Randomized controlled trials in patients with NMD in the future would help to establish a higher level of evidence.

Future directions of research in this area include understanding the interval of PFT testing based on the rate of disease progression for an individual NMD, the use of end-tidal or transcutaneous CO_2 monitoring in the detection of hypoventilation in outpatient settings, the role of polysomnography in the diagnosis of NMD, understanding the impact of telemedicine in the management of NIV prescription and monitoring, use of device downloads to modify the NIV prescription, use of artificial intelligence for automatic adjustment of device settings, modernizing and easing access to ventilation support for patients with NMD, comparison of outcomes of airway clearance and secretion management techniques such as MI-E and LVR, and comparison of tracheostomy with MPV. Additionally, data are needed to help modernize and improve access to ventilatory support for patients with NMD and to understand better the role of shared decision-making with patients with NMD in enhancing quality of life and long-term outcomes.

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