CANADIAN JOURNAL OF RESPIRATORY, CRITICAL CARE, AND SLEEP MEDICINE
https://doi.org/10.1080/24745332.2018.1559644

Taylor & Francis
Taylor & Francis Group

CTS GUIDELINES AND POSITION PAPERS

Home mechanical ventilation for patients with Amyotrophic Lateral Sclerosis: A Canadian Thoracic Society clinical practice guideline

Karen P. Rimmer[a], Marta Kaminska[b], Mika Nonoyama[c], Eleni Giannouli[d], François Maltais[e], Debra L. Morrison[f], Colleen O'Connell[g], Basil J. Petrof[h], and Douglas A. McKim[i]

[a]University of Calgary, Calgary, Alberta, Canada; [b]Research Institute of the McGill University Health Centre, Montréal, Québec, Canada; [c]University of Ontario Institute of Technology, Oshawa, Ontario, Canada; [d]University of Manitoba, Winnipeg, Manitoba, Canada; [e]Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec, Québec, Canada; [f]Sleep Disorders Clinic, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada; [g]Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, Canada; [h]Meakins-Christie Laboratories, McGill University Health Centre, Montréal, Québec, Canada; [i]Division of Respirology, University of Ottawa and The Ottawa Hospital Research Institute, CANVent Respiratory Services, Ottawa, Ontario, Canada

ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder involving both upper and lower motor neurons that results in progressive weakness of skeletal muscles. Regardless of site of first onset, death usually occurs as a result of progressive respiratory muscle involvement, with 50% of patients dying within three years of symptom onset. Mechanical ventilation is becoming increasingly accepted in ALS. In Canada, noninvasive ventilation is the most common form of ventilation applied, with tracheostomy ventilation being very uncommon. The current guideline addresses respiratory muscle testing, the benefits of mechanical ventilation in ALS, timing of initiation of ventilation and modes, settings and place of initiation. It also reviews diaphragm pacing and respiratory muscle training. Finally, given the challenges involved with tracheostomy ventilation in ALS, the question of tracheostomy ventilation is addressed.

RÉSUMÉ

La sclérose latérale amyotrophique est une affection neurodégénérative impliquant les neurones moteurs supérieurs et inférieurs qui résulte en une faiblesse progressive des muscles squelettiques. Indépendamment de la première région du corps où elle se manifeste, elle entraine habituellement la mort en raison de l'implication progressive des muscles respiratoires : 50% des patients meurent dans les trois ans suivant l'apparition des symptômes. La ventilation mécanique est de plus en plus acceptée dans les cas de SLA. Au Canada, la ventilation non invasive est la forme la plus commune de ventilation appliquée, tandis que la trachéotomie est très rare. Cette ligne directrice porte sur l'évaluation des muscles respiratoires, les avantages de la ventilation mécanique dans les cas de SLA, le moment où commencer la ventilation, les modes de ventilation, le paramétrage et le lieu où débuter la ventilation. Elle aborde aussi la stimulation du diaphragme et l'entraînement de la musculature respiratoire. Finalement, étant donné les défis que présente la ventilation par trachéotomie dans les cas de SLA, la question de la ventilation par trachéostomie est aussi abordée.

KEYWORDS

Amyotrophic Lateral Sclerosis; home mechanical ventilation; respiratory muscle weakness

Introduction

The first Canadian Thoracic society (CTS) guideline for Home Mechanical Ventilation (HMV) was published in 2011[1] and included a section detailing recommendations for HMV for patients with Amyotrophic Lateral Sclerosis (ALS). This is the first update of the ALS section of that guideline and is intended for use as a standalone document making recommendations on the respiratory care of ALS patients. It excludes airway clearance and recruitment techniques in ALS and other neuromuscular disorders that were addressed in the 2011 guideline and that will be covered in an upcoming update by the CTS HMV clinical assembly. Airway clearance and recruitment are recognized to be of critical importance in the care of ALS patients.

ALS is a neurodegenerative disorder involving both upper and lower motor neurons that results in progressive weakness of skeletal muscles. Generally, onset of weakness is characterized as either limb or bulbar. Less commonly, approximately 3% of ALS cases in referral centres, the first presentation is with respiratory symptoms secondary to early respiratory muscle involvement.[2,3] Regardless of site of first onset, death usually occurs as a result of progressive respiratory muscle involvement, with 50% of patients dying within three years of symptom onset.[4] Patients with bulbar onset ALS generally have a shorter survival than those with limb onset.[5] The rapid progression to death separates ALS from most other neuromuscular disorders (NMDs) for which noninvasive ventilation (NIV) and tracheostomy ventilation are considered. ALS is also distinct from other medical

CONTACT Karen P. Rimmer karenp.rimmer@albertahealthservices.ca Peter Lougheed Hospital, 3500-26 Ave NE, Calgary, Alberta, Canada T1Y 6J4.

conditions for which chronic mechanical ventilation is provided, including other neuromuscular disorders (NMDs), by virtue of having the poorest survival using ventilation. In one case series, only 5% of ALS patients using mechanical ventilation were alive after five years, as compared to more than 60% of patients with other neuromuscular diagnoses.[6]

Ninety-five percent of the ALS patients using home ventilation in the Swedish Home Mechanical Ventilation registry[6] were using it noninvasively, a number similar to data from the North American ALS CARE database, which has remained largely unchanged since 1996 when it was created.[7]

Use of home ventilation is increasing despite some debate regarding the ethics of prolonging survival in such a rapidly progressive disorder with poor survival on NIV.[6] In 1999, Melo published a survey of multidisciplinary ALS clinics and found that only 15% of eligible patients were using NIV.[8] This number was similar to that reported in the ALS CARE database two years later.[9] The ALS CARE database was reviewed again in 2006, following many reports of positive outcomes with the use of NIV and found that 36.2% of patients considered to be candidates were using NIV.[10] A Canadian survey of ALS centres published in 2010 found that NIV was used by 18.3% of patients, while only 1.5% were reported as tracheostomy ventilated.[11]

The increasing trend in use of NIV in ALS was highlighted by a 2012 publication reviewing the UK experience.[12] They noted a 3.4 fold increase in NIV use in ALS between 2000 and 2012. An Australian database reporting on a large cohort of patients with ALS found 23% of their patients between 1991 and 2011 received NIV.[13] Some countries have reported particularly high incidences of NIV use. A recently published Japanese study reported that 52% of their patients used NIV after 2000.[14] Finally, a single center report from Denmark also reported a high incidence of 42.3% treated with NIV between 1998 and 2012.[15] Although there may be variability in its use, the focus in the ALS literature now is not whether or not to offer NIV, but rather the optimal timing and criteria for initiation of NIV.

Differences from prior guideline published in 2011

This clinical practice guideline is an update from an earlier guideline that was published in 2011 by the Canadian Thoracic Society.[1] Changes in the content from the prior guideline include the following:

1. Further reports of the benefits of HMV.
2. New techniques to evaluate respiratory muscles are discussed, and reevaluation of previously reported respiratory testing.
3. Exploration of the rationale for earlier timing, with less focus on a cut off value for vital capacity.
4. Review and recommendations regarding respiratory muscle training in the ALS population.
5. More conclusive evidence regarding diaphragm pacing after publication of two randomized controlled trials (RCTs) showing negative outcomes.
6. Recommendation of mouthpiece ventilation as an option in a subgroup of ALS patients.
7. Exclusion of any discussion of airway clearance in ALS. This is recognized to be of critical importance, was addressed in the 2011 guideline,[1] and is currently under review by the HMV clinical assembly.

Target patient population

The current clinical practice guideline applies to all adult individuals with Amyotrophic Lateral Sclerosis who are at risk for or are using HMV.

Target users

The present clinical practice guideline is intended for use by the health care teams that care for individuals who are at risk for or require ventilatory assistance. Respirologists, physiatrists, neurologists, family practitioners, nurses, respiratory therapists, physiotherapists and other health care professionals can use this guideline to help inform their clinical practice with regard to HMV. This guideline is also intended for use by ventilator-assisted individuals (VAIs) and their caregivers to help them make informed decisions on HMV and by health care decision makers to aid in establishing policy and making funding decisions.

Guideline panel composition

The CTS HMV guideline panel was interprofessional and was comprised of HMV clinicians and health care professionals with content expertise. The panel was chaired by one author and included seven adult respirologists, one physiatrist specializing in neurorehabilitation and one registered respiratory therapist. All author conflicts of interests are posted on the CTS website at https://cts-sct.ca/guideline-library/. Patient and caregiver input was not sought in development of this guideline, which is a weakness of the current guideline and which will be corrected in the next update of this document.

Methodology

This clinical practice guideline was developed in accordance with the CTS guideline production methodology (https://cts-sct.ca/guidelines). The panel utilized the AGREE II checklist[16] to guide the development of this guideline.

Selection of key clinical questions: The primary author and the chair of the guideline panel determined key clinical questions based on their own knowledge of the literature and existing guidelines in the areas of benefits of mechanical ventilation in ALS; respiratory muscle testing and monitoring; timing of initiation of ventilation; modes, settings and place of initiation; diaphragm pacing; respiratory muscle training; and tracheostomy ventilation. Draft questions were then reviewed, discussed and revised by the panel with the final questions chosen to address significant changes since the last guideline, and gaps not addressed by prior guidelines in the area of ALS care. Using the PICO method, the panel took into consideration the

Patient group or groups that should be addressed, the **I**ntervention or interventions that should be examined, the **C**omparison groups that should be part of the studies of the various interventions and the **O**utcome or outcomes of interest. In the second part of the PICO process, panel members were asked to consider issues that influence implementability, when choosing PICO questions: the magnitude of the knowledge-to-care gap; target audiences; known barriers and supports to implementation; societal impact; and measurability of any implementation program. Members reached consensus on these questions over several teleconference meetings, webinars and email exchanges.

Literature search and screening of abstracts: An initial literature search was completed current to September 2017 using MEDLINE (OVID); Embase (OVID); HealthStar; the Cochrane Library: the Canadian Medical Association InfoBase; and the National Guideline Clearinghouse. The second literature search was conducted through to March 31, 2018 to include the most recent literature. Additional articles were found by review of the references in the articles accepted. Details of the search strategy are outlined in Appendix 1. The abstracts were assessed independently by two panel members for inclusion or exclusion and conflicts were resolved by discussion between panel members.

Study selection criteria: Following the completion of the abstract screening, the full text articles were retrieved and reviewed. Articles were selected for inclusion in the systematic review if they were directly relevant to one of the six PICO questions. All types of reports were considered and included guidelines, meta-analysis, systematic review, randomized controlled trial, cohort study, case control study, case series or case report.

Critical appraisal of identified studies: Data from all articles relevant to each PICO question were abstracted into tables by the lead author and can be found on the CTS website, at https://cts-sct.ca/guideline-library/. During discussion of each question via webinars held in June and July of 2018, the data were reviewed by the panel, and evidence addressing each clinical question was assessed according to the components of the GRADE[17] criteria (Table 1).

***Synthesis of evidence-based clinical judgement of risk versus clinical benefit*:** For each clinical question, the panel considered the strength and directness of the published evidence supporting an intervention or treatment approach. The panel discussed the potential health benefit to the patient, the overall impact on the population burden of morbidity and mortality of ALS, and issues of risk, burden on a patient to adhere and cost effectiveness of an intervention or treatment. These discussions and the resulting synthesis of clinical judgement are presented for each recommendation.

Clinical remarks are included in association with each clinical question and are intended to offer experienced advice to the target user. Some of these good practice points

Table 1. Strength of the recommendations grading system.

Grade of Recommendation		Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	1A	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	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	1B	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	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- or very-low-quality evidence	1C	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	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 recommendation, high-quality evidence	2A	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate effect.
Weak recommendation, moderate-quality evidence	2B	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient 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 recommendation, low- or very-low-quality evidence	2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	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.

Table 2. Voting scales for assessing consensus on draft recommendations.

First round of voting	1. Wholeheartedly agree
	2. Agree
	3. Can support
	4. Reservations – would like more discussion
	5. Serious concerns – needs more discussion
	6. Cannot participate – block it
Second round of voting	1. Agree
	2. Can support
	3. Cannot support – block it

For a recommendation to be accepted, it has to be voted on by 75% of the eligible panel members and achieve ratings of wholeheartedly agree, agree, or can support by 80% of the voting panelists. If this is not achieved, additional discussion and revision of the recommendation(s) ensues, for which acceptance of a recommendation requires a majority (80%) for option 1 or 2.

may not have an evidence base, but are viewed as good clinical practice by the expert panel. All good practice points were arrived at by consensus, based on the clinical experience of the guideline panel members.

Formulation of recommendations and classification: Following the open and extensive discussions and review of evidence for each PICO question, a draft recommendation was proposed. The strength of the recommendation was based on consideration both of the GRADE quality of evidence, and the expert panel's synthesis of clinical judgement. In accordance with CTS methodology, the recommendations were then reviewed by the CTS Canadian Respiratory Guideline Committee (CRGC) Chair to optimize the language of each recommendation with a view to improving intrinsic implementability.[18] Next, a recommendation consensus process was completed by electronic survey using a six-point voting scale (Table 2). For a recommendation to be accepted, it had to be voted on by 75% of the panel members and achieve ratings of "wholeheartedly agree," "agree" or "can support" by $\geq$ 80% of the voting panelists. In the event of a failure to reach this threshold, another period of discussion ensued, whereby dissenting opinions were heard and considered. The recommendation was then revised, followed by a second round of electronic voting using a three-point scale (Table 2), with acceptance of a recommendation requiring $\geq$ 80% of the voting panelists choosing option 1 or 2. Through this process, all recommendations achieved acceptance, with a second round of voting required for only 3/22 recommendations.

Applicability

Facilitators and barriers to its application: The tools exist for implementation of the recommendations of this guideline. Equipment is readily available and provincially funded in Canada in most, though not all, provinces and territories and the minimum required monitoring can be performed in both large and small centres. Unfortunately, not all ALS patients are cared for in multidisciplinary ALS clinics and, in ALS clinics, the model of respiratory care is inconsistent. This may be a barrier to application.

Advice and/or tools on how the recommendations can be put into practice: Optimally, all ALS patients should be regularly followed in multidisciplinary ALS clinics with experienced respiratory therapists and respirologists; however, this may not be an immediately achievable goal. Protocolizing follow up and respiratory monitoring for ALS patients, whether followed by individual respirologists, neurologists or family physicians, can identify patients requiring intervention leading to timely initiation of noninvasive and the positive outcomes detailed in this document.

Registered Respiratory Therapists (RRTs) are excellent resources and individual health regions should be encouraged to capitalize on their expertise. Busy respirologists have come to rely on RRTs in health regions where they are trained to initiate and monitor noninvasive ventilation in association with a clinic specializing in HMV. RRTs alert team members to changes in status and needs and can be an excellent "early warning" system of a failing respiratory status in the ALS population. Health regions should be lobbied to include experienced RRTs in their ALS clinics and home care teams. The RRT community resource can be used for other ventilated and at risk populations making it valuable for a larger number of individuals.

Potential resource implications of this guideline: Excellent and timely care of the ALS population has the potential to reduce acute care needs and overall cost to the system. The equipment is already currently funded in most jurisdictions and the equipment costs are minor when compared to inpatient admission costs. The cost of adding newer monitoring equipment (eg, Sniff Nasal Inspiratory Pressure monitor) is small and can be absorbed by most of the larger centres.

Monitoring and/or auditing criteria: As care of the ALS patient may be by individual neurologists, respirologists or ALS centres, it will be challenging to monitor adoption of the guideline. The most reliable data collection at present is by ALS clinics and by the Canadian ALS Research network and it is for this reason that a survey of awareness and compliance will be done through ALS clinics and the Canadian ALS Research network. At 12–24 months post publication and distribution, ALS clinics across Canada will be surveyed to assess their knowledge of and compliance with recommendations.

Review and approval process

In accordance with the CTS guideline review and approval process, before completion, CTS staff distributed the guideline for formal review by: 1) two international ALS content experts); and 2) two internal (CTS) reviewers with one reviewer performing an AGREE assessment of the guideline. The authors were blinded to the identities of the reviewers. The lead author considered AGREE II scores and reviewer comments, provided responses to the comments, and made corresponding changes to the manuscript. These reviews and the AGREE II scoresheet were provided to the CTS CRGC for review. The CRGC then reviewed these documents and provided further suggestions for edits that were considered by authors. The CRGC then recommended approval of a final draft of the guideline to the CTS Executive Committee. All reviews and author responses are posted on the CTS website at https://cts-sct.ca/guideline-library/.

Living guideline/future updates

The HMV ALS guideline PICO questions will be uploaded in the CTS/McMaster Database, whereby authors will use the continuously updated McMaster Plus database to review

new articles pertaining to these PICO questions published in top impact-factor journals as of April 2018. The studies are indexed according to the PICO questions, and made available to the guideline panel on a dedicated software platform for manual assignment to individual reviews. This evidence service will prompt guideline updates and facilitate year end reviews. The entire guideline will be reviewed every three years or sooner, to determine the need for guideline updates, in accordance with the CTS Living Guideline Model (details available at www.cts-sct.ca/guideline-library/).

Summary of evidence

Section 1. Assessment of benefit of Non-Invasive ventilation in ALS

PICO 1: Does noninvasive ventilation as compared to best practice without noninvasive ventilation result in improved:

1. Survival
2. Quality of Life or
3. Physiologic measures?

Survival

The only randomized controlled trial (RCT) of noninvasive ventilation (NIV) with survival as a primary outcome was published by Bourke et al in 2006.[19] They screened 121 patients and ultimately recruited 92 patients to be followed every two months until randomization, which occurred if they met one or both of the pre-defined criteria: orthopnea with Peak inspiratory pressure (PImax) less than 60% predicted or symptomatic daytime hypercapnia. Ultimately, 41 were randomized and the data analyzed for all patients and also subdivided into "better" or "poor" bulbar function. All patients using NIV showed a modest survival advantage from randomization to death over those patients randomized to standard care excluding NIV: 219 (range 75–1382) days vs 171 (1–878) days. The subgroup with "better" bulbar function showed a much larger survival advantage with NIV compared to controls: 216 (range 94–681) days vs. 11 (1–283) days. There were six deaths of nine patients in the control group with better bulbar function within two weeks of enrollment. Five of the six had severe respiratory muscle weakness at enrollment. The "poor" bulbar function group showed improvement in health-related quality of life (HRQoL) if receiving NIV, but no survival benefit: 222 (range 75–1382) days vs 261 (6–878) days. The mean duration of daily use in this group, however, was less than four hours. In addition, the numbers were small and not powered to show survival benefit in the subgroup with poor bulbar function.

The Cochrane database of systematic reviews recently updated their review of mechanical ventilation in ALS in 2017[20] and found no new RCTs in this population addressing survival, disease progression or HRQoL. At the conclusion of their review, they commented that "more RCT evidence to support the use of NIV in ALS will be difficult to generate, as not offering NIV to the control group is no longer ethically justifiable." They commented that future studies should focus on the timing of initiation of NIV for maximal benefit.

Other prospective studies[6,21–23,24] and retrospective studies[13–15,25–27] have reported prolonged survival in those using NIV. None of these studies was randomized, although attempts were made to provide a control group. The controls included patients refusing or intolerant of NIV or those using NIV less than 4 hours/day.[13,22–24,26,28] Historical controls were also considered.[29]

An Australian group[13] reported the largest cohort of patients (n = 929), 23% of whom received NIV. They found a survival advantage in patients treated with NIV, surviving 28 months from symptom onset as compared to 15 months in those who did not receive NIV. Interestingly, the subgroup demonstrating the clearest survival benefit was the bulbar onset group with a 19 month survival advantage, which is in contrast to most other studies reporting NIV outcomes in patients with severe bulbar dysfunction. One other recent study did, however, report a clear survival advantage in patients with severe bulbar dysfunction.[24] Numbers of bulbar patients were small (n = 15 NIV vs n = 6 controls) in this study. The control group was comprised of patients declining NIV. More severe bulbar dysfunction, as measured by the Norris Bulbar Score, was a prognostic factor in NIV failure, although a cut off value of the Norris Bulbar Score was not suggested. Despite this, prolonged survival from disease onset was found in the severe bulbar group with NIV: 40 months in the NIV group vs 16 months in those refusing NIV. This suggests that those accepting and tolerating NIV with severe bulbar dysfunction show a significant survival benefit.

The survival benefit was modest in most of the reported studies; however, in one retrospective descriptive study reported by Bach's group[27] the survival benefit in a subgroup of patients with preserved bulbar function could be measured in years even when requiring continuous NIV.

Quality of life

In the single RCT of NIV in ALS,[19] improved HRQoL was reported for patients randomized to NIV compared with standard care with no NIV. For those with "better" bulbar function, NIV resulted in large improvement across several measures of HRQoL when compared to controls. Patients with "poor" bulbar function randomized to NIV also showed improvement in HRQoL, although the improvement was less marked.

In other prospective studies reporting HRQoL,[21,23,30–33] authors consistently reported improvements in HRQoL in certain domains for patients using NIV. These included sustained improvements in mental health, energy/vitality, social isolation, fatigue and mastery. Physical function domains generally worsened as would be expected with disease progression.

Gas exchange and pulmonary function

All studies reporting gas exchange after initiation of NIV[31,32,34–36] show reduction of daytime partial pressure of carbon dioxide (pCO2) after initiation of nocturnal ventilation.

Five studies have reported the rate of decline of vital capacity (VC) before and after initiation of NIV.[13,23,27,28,30] Four of these studies[13,27,28,30] showed a slowing of decline of lung

function after successful initiation of NIV, while in contrast, one study[23] reported a decrease in VC after initiation of NIV.

Sleep

There are many reasons for sleep disruption in patients with ALS. Limited ability to change body position, pain and anxiety may all be factors. As with other neuromuscular disorders that involve respiratory muscles, sleep fragmentation by breathing related arousals has been reported. Early studies looking at sleep in patients with ALS sought to characterize the nature of the sleep disturbance that occurred, with recent studies looking more systematically at the effect of NIV on sleep parameters and HRQoL. Seven early studies that characterize breathing related sleep abnormalities specifically in patients with ALS[25,34,37–41] reported a decrease in total sleep time and sleep efficiency, increased stage 1 sleep and reduced REM sleep. The predominant pattern of sleep disordered breathing was not obstructive apneas, but rather, mixed apneas, central apneas and hypoventilation. Among these studies patient selection varied widely. In two of the studies,[25,34] patients selected had more advanced disease, with either very low VC (mean 52%) or symptoms suggesting sleep disordered breathing. Patients in other studies were asymptomatic[39] or had normal pulmonary function and diaphragm function.[41]

Given bulbar involvement by ALS, the possibility of upper airway obstruction during sleep has been raised. Ferguson et al[38] found obstructive apneas did not occur; however, other investigators have noted obstructions in some subjects.[42–44]

In four of the seven early studies,[25,34,37,38] at least one subject was treated with NIV. Observations included improvement in sleep architecture, decreased breathing related arousals, improved oxygenation during sleep and improved symptoms related to sleep disordered breathing. In another,[31] cognitive impairment improved after NIV and was assumed to be related to correction of sleep disordered breathing.

More recent studies have reported the effect on HRQoL and sleep parameters with NIV. Sustained improvement in the Epworth Sleepiness Scale (ESS) and Pittsburg Sleep Quality Index (PSQI) and some subscales of the McGill QoL (MQoL) questionnaire were found and scores did not fall below baseline despite worsening ALSFRS scores.[36] One author[42] reported on the effect of NIV on sleep and showed that the minimum saturation improved by 7% with NIV. Time spent <90% also improved with NIV though other sleep parameters showed no significant change (sleep efficiency, AHI, arousal index or sleep architecture). Another report[45] found that those with bulbar dysfunction had better quality sleep at baseline with less change noted after NIV initiation compared to non-bulbar patients. PSQI did improve in bulbar patients though improvements in ESS, and MQoL were observed only in non-bulbar patients. In the entire cohort, N3 sleep and REM increased and arousal-awakening index (AAI) improved. The short form survey (SF-36) emotional health subscale also improved. A later report by the same authors[46] studied patient ventilator asynchrony, leaks and sleep quality. They noted the commonest asynchrony was ineffective efforts and that despite meticulous titration, patient ventilator asynchrony and leaks persisted, although interestingly, had a minor impact on sleep.

Box 1. Assessment of Benefit of Non-Invasive Ventilation in ALS

PICO 1: Does non-invasive ventilation as compared to best practice without non-invasive ventilation result in improved:

1. **Survival**
2. **QoL or**
3. **Physiologic measures?**

Conclusions

NIV, as compared to standard care excluding NIV, improves survival, some domains of HRQoL and some physiologic and sleep parameters. Bulbar predominant or severely involved, and non-bulbar ALS patients may have different survival advantages with NIV, but the literature would support its use in both bulbar and non-bulbar patients.

Recommendation:

1. We recommend NIV for patients with ALS meeting initiation criteria specified in PICO 2.2, provided it is in keeping with patient preferences and values (GRADE 1B)

Clinical remarks:

It is imperative that the patient's own wishes, beliefs and goals of care be clarified when NIV is being considered. It should be made clear that this is a therapeutic option that can be refused or discontinued at any time in accordance with the patient's wishes. Bulbar dysfunction should not preclude consideration of NIV therapy. The benefits found in the literature are reported with nocturnal initiation, with the extension of use into daytime assumed with disease progression though generally not explicitly stated.

Section 2. Respiratory testing in ALS and timing of NIV initiation

PICO 2.1) What type of testing is required to predict survival, respiratory failure or need for home mechanical ventilation/noninvasive ventilation?

2.2) What criteria should be used for initiation and monitoring of noninvasive ventilation to optimize benefit?

Respiratory testing

Measuring lung function in ALS serves two purposes. First, it has been shown that some measures of lung function are better predictors of survival than functional rating scales.[5,6,47,48] This information could facilitate the design of studies evaluating new therapies, such as medications, in order to enrich the study population, possibly requiring fewer patients to achieve significance and aid in sample size calculations. Second, monitoring lung function helps guide the timing of interventions such as initiation of NIV.

Earlier literature focused on measures of lung function which predicted daytime hypercapnia, a logical criterion to initiate mechanical ventilation. More recently, however, there has been a focus on predicting nocturnal sleep disordered breathing for the purpose of earlier initiation of ventilation before onset of daytime hypercapnia with the goal of improving outcomes such as survival or HRQoL.

An earlier study looked extensively at predictors of daytime hypercapnia.[49] It assessed VC, FEV1, peak inspiratory pressure (PImax), peak expiratory pressure (PEmax), sniff transdiaphragmatic pressure (Pdi), sniff esophageal pressure (Poes), sniff nasal pressure (SNP), cough gastric pressure (Pgas), bilateral cervical magnetic stimulation (CMS) Pdi and arterial blood gas (ABGs). Sniff Pdi and CMS Pdi had the greatest predictive power for the presence of daytime hypercapnia. Of the less invasive tests, Sniff nasal inspiratory pressure (SNP) had the best predictive power. This predictive power was limited to those patients without significant bulbar dysfunction. No test reliably predicted hypercapnia in the patients with bulbar dysfunction.

Hypercapnia, though a relatively late finding, remains an indication for initiation of HMV and can be determined by ABG, or capillary blood gas[50] or transcutaneous CO2.[51,52]

A more recent assessment[53] of the predictive power of invasive and noninvasive respiratory muscle strength assessments for survival or ventilator free survival showed that VC had a good predictive power, but the cutoff value for a good outcome was in the normal range (>80% predicted) for all time intervals beyond 3 months. Although all tests of muscle strength predicted ventilator free survival, they had varying sensitivities. Sniff and Twitch transdiaphragmatic pressure were the best performing tests for ventilator free survival, although SNP also was shown to have a good predictive value. Maximal expiratory pressure (MEP) and MEP% predicted were also useful predictive tests. Supine forced vital capacity (FVC) was not assessed.

SNP has gained popularity in assessing the respiratory muscles as it is more sensitive to early muscle weakness than FVC[54] and can be performed by most patients, even those with advanced disease and bulbar dysfunction.[55]

A SNP less (reduced strength[1*]) than -40 cmH2O was shown to be significantly correlated with nocturnal hypoxemia and patients at this level had a median survival of only 6 months.[54] A more recent study[56] looked at SNP and other measures of lung function, including FVC, for predicting death at one year. A SNP < -50 cmH2O was more likely to be associated with death at one year and a SNP of > -70 cmH2O resulted in improved survival at one year. Ultimately a SNP cutoff value of -34 cmH20 was found to have a sensitivity of 0.75 and a specificity of 0.72 for death at one year. The highest risk of death at one year was found in those with a sniff nasal pressure ≤ -18cmH2O. By comparison, the cut off value for FVC to predict death at one year was high at 75.9% and was less predictive for death at one year than SNP.

Maximal inspiratory pressure (MIP) is also a sensitive measure of early muscle dysfunction and can be used as the disease progresses to predict survival, but requires the patient to tolerate and be able to seal around the mouthpiece, or mask in order to perform the test.[53,57]

Sitting VC is an insensitive measure of respiratory muscle weakness as it may remain normal even when respiratory muscle weakness is present. However, in one older study, when FVC falls to less than 50% predicted, survival was limited to nine months with most patients dying by six months.[47] Other authors have also noted the poor prognosis of patients with FVC < 50% predicted[48,58] and, therefore, it is recognized that FVC, when very low, is specific for impending respiratory failure and death. It has become increasingly recognized that sitting FVC or SVC are not the best predictors of muscle weakness and impending respiratory failure given that FVC may be normal or near normal when other measures of respiratory muscle strength may be significantly abnormal.[53,56,59] More sensitive to respiratory muscle weakness and diaphragmatic dysfunction, in particular, is supine VC. A correlation between the percentage fall in VC from the erect to the supine position and the lowest saturation during REM sleep[60] suggests that a drop in VC from the erect to the supine position may be used to predict abnormalities in breathing during sleep associated with diaphragm dysfunction. Others have found that the change in VC from the erect to supine posture correlates well with symptoms of dyspnea, orthopnea and daytime fatigue.[61] A normal supine FVC was highly predictive of survival at 2 years.[62] Another author found a Borg dyspnea scale ≥3 when supine to be a useful predictor of a SNP ≤-40 cmH2O and impending respiratory failure.[63]

Rate of decline of Slow Vital Capacity (SVC) has also been assessed[64] and shown to be strongly correlated with rate of decline of SNP and respiratory symptoms. The probability of respiratory failure free survival was estimated in this study by the rate of decline in the SVC suggesting that this is a useful prognostic tool. The finding of rate of decline of respiratory tests as a prognostic tool was confirmed by another study,[57] which looked at decline in VC, MIP or SNP, MEP and PCF and showed that the risk of death is significantly associated with the decline in pulmonary function regardless of the PFT parameter followed.

More recently the amplitude of the action potential with phrenic stimulation has been correlated with pulmonary function tests, symptoms and survival at one year.[65] When the amplitude of the action potential (Pamp) was < 0.3mV, the median survival was 1.07 years as compared to a Pamp > 0.3mV of greater than 2 years. It was also found that a Pamp < 0.3mV correlated with symptoms of dyspnea, orthopnea and tachypnea. This threshold value of Pamp was also correlated with reduced FVC, MIP and SNP. Another study[66] also found that an abnormal Pamp was a predictor of death using a cutoff value of 0.4mV with a HR of 1.653 for those with a Pamp of <0.4mV. This is a non-volitional test and could aid in defining populations for future interventional studies in ALS.

Given the difficulty with volitional tests in this population, in particular the bulbar predominant patients, other non-volitional tests have been investigated. Diaphragm thickness by ultrasound has been found to correlate with other tests of respiratory function and to the compound muscle action potential (CMAP) of the diaphragm.[67,68] This correlation, unfortunately, was less evident in patients with bulbar dysfunction and relatively mild symptoms, a population in which it may have been particularly helpful.

Lung function is essential in the follow-up of ALS patients, but equally important is a history that focuses on symptoms

[1]*In this document, less refers to reduced strength, ie, −20cmH20 is considered less than −40.

of dyspnea, orthopnea, poor sleep, excessive daytime sleepiness, morning headache and fatigue. The onset of dyspnea and rate of decline of VC predicted survival in one series.[69] Excessive daytime sleepiness and poor sleep were very good in predicting sleep disordered breathing, though not specific enough to use alone. Finally, orthopnea was found in one study[34] to be a good predictor of sleep disordered breathing.

An excellent review of Respiratory measures in ALS was recently published by Lechtzin et al, which summarizes much of the aforementioned information.[70]

Timing of initiation of NIV

Early studies demonstrating the benefit of NIV in ALS patients with daytime respiratory failure have questioned whether earlier initiation of ventilation improves rate of decline in respiratory function, survival and HRQoL. Investigators have sought to define the optimal timing of initiation of NIV to maximize benefit.

Five earlier studies[29,30,33,69,71,72] addressed the issue of timing. Many other studies speak indirectly to this question as the indications for initiation of ventilation may include symptoms alone without the requirement for an abnormal measure of lung function or hypoventilation.[22,23,26,28,30] Orthopnea is often the symptom for which ventilation is started.[21–23,25,26,71] A study by Bourke et al.[30] supported initiation of ventilation for symptoms. They reported the greatest benefit and compliance in patients who complained of orthopnea. Also, in support of symptoms as an inclusion for initiation, they reported that four patients were initiated on NIV for the sole indication of nocturnal desaturation without symptoms. Of the four patients, only one was compliant with NIV and continued to use it.

A study exploring earlier initiation of NIV looked retrospectively at the survival of patients in whom NIV was started when FVC was greater than 65% predicted.[72] There were 67 patients in the standard therapy group and 25 in the early initiation group. There was a survival benefit from time of diagnosis to death in those starting NIV with FVC $>$ 65% of predicted. Of note, however, the authors comment that patients in the "early" group frequently, though not always, had pulmonary function or ABG abnormalities that would have qualified them for NIV by other conventional measures.

In another study,[29] historical controls who received NIV for diurnal respiratory insufficiency were compared to ALS patients screened every three months with nocturnal oximetry and initiated on NIV when they demonstrated more than 15 periods of nocturnal desaturation per hour. The authors reported that survival was improved if NIV was started with evidence of nocturnal sleep disordered breathing, and prior to daytime blood gas abnormalities. However, for the subgroup with bulbar dysfunction, there was no survival benefit. The concept of NIV applied for nocturnal desaturation to improve survival, lead to studies which attempted to predict the presence of nocturnal disordered breathing or nocturnal desaturation or hypoventilation allowing for earlier initiation. Polygraphy was compared to FVC and symptoms.[59] This investigation suggested that the correlation between symptoms or FVC and the presence of nocturnal hypoventilation, as defined by prolonged desaturation or a nocturnal capillary pCO2 $>$ 45, was poor. Eight of their 131 patients had FVC $<$ 50% predicted and demonstrated no hypoventilation. In contrast, 14 of the 29 patients with FVC $>$ 75% of predicted with no symptoms of dyspnea, demonstrated nocturnal hypoventilation. It is not clear whether treatment of these asymptomatic patients with a normal or near normal FVC who demonstrate nocturnal hypoventilation will improve their survival or QoL.

A recent pilot, placebo controlled study looking at early NIV[73] demonstrated the feasibility of use of sham ventilation in their study design. They defined early as FVC $>$ 50% and demonstrated no difference between groups in their study though, to ensure tolerance, pressures were very low with an inspiratory positive airway pressure (IPAP) of only 8 cm.

Timing of NIV initiation has also been indirectly addressed by the recent literature which focused more on patient factors or testing that predict survival with NIV, predictors of tolerance to NIV, the effect of NIV on sleep and models for initiation of NIV which improve outcomes.[36,42–45,74,75–77] These studies imply both indications and timing that should be used for ventilation by demonstrating positive outcomes with the protocols applied.

Monitoring post initiation of NIV

Assessment of successful NIV has historically involved improvement in symptoms and gas exchange. More recently device download and assessment of nocturnal saturation or tCO2 have been reported. Two recent papers[43,44] focused on the effect of NIV in correcting nocturnal desaturation and obstructions on survival. In both studies, device download was a component of post initiation monitoring of successful ventilation. One study[43] found better survival in those with a saturation $>$90% for $>$95% of the night while on NIV when assessed at 1, 3 and 6 months after initiation. If the study participant was found to have persistent desaturation at 1 month after initiation of NIV, changes were made in an attempt to correct the desaturation. This was reassessed again at 3 and 6 months. In those that were corrected at 1, 3 or 6 months, survival was reported to be the same as those who were well ventilated at 1 month. Device download assisted in the evaluation of the leak, which was a component in the correction. In the subset of patients who could not be corrected, survival was shorter. A follow-up study[44] looked at obstructions as a cause for desaturations and found that those with persistent obstructions had a shorter survival than those without obstructions. This was the case even if the obstructions were not associated with desaturation. They concluded that the effectiveness of ventilation is important to survival.

Section 3. Tracheostomy ventilation in ALS

PICO 3: Compared with NIV alone, does tracheostomy/invasive ventilation with or without preceding NIV:

1. Prolong survival
2. Provide an acceptable QoL
3. Result in excessive caregiver burden?

Box 2. Respiratory Testing in ALS and Timing of NIV initiation

PICO 2.1: What type of testing is required to predict survival, respiratory failure or need for home mechanical ventilation/noninvasive ventilation?

PICO 2.2: What criteria should be used for initiation and monitoring of non-invasive ventilation to optimize benefit?

Conclusions
Many physiologic parameters including FVC, SVC, supine VC, MIP/MEP, SNP, PCF and CMAP on phrenic nerve stimulation have been correlated with survival and help to predict respiratory failure. A single parameter has not been identified as the most useful or predictive respiratory measure. Regular monitoring has been recommended to follow the decline in respiratory muscle function with most studies recommending repeated testing every 3 months. Recognizing the differences in rate of disease progression, regular monitoring every 2 to 6 months would be recommended. Nocturnal monitoring prior to initiation of NIV may be helpful in determining timing of NIV initiation though there is currently inadequate evidence to support regular and repeated nocturnal monitoring as part of routine follow-up. Follow-up with nocturnal assessment of oxygen saturation and device download to determine effectiveness of ventilation may prolong survival if effective ventilation can be achieved.

Optimal timing for NIV for maximal benefit has yet to be determined. Current literature supports initiation for the indications listed in PICO 2.2 recommendations.

PICO 2.1: What type of testing is required to predict survival, respiratory failure or need for home mechanical ventilation/non-invasive ventilation?

Recommendations:

1. We recommend regular monitoring of ALS patients every two to six months from time of diagnosis (consensus based), depending on the anticipated rapidity of disease progression, including the following:

(a) Symptom review to include orthopnea, dyspnea, poor sleep, excessive daytime sleepiness, poor concentration, morning headache (GRADE 1C)

(b) Measurement of sitting FVC or SVC (GRADE 1B)

(c) Measurement of one or more of the following as a more sensitive measure of inspiratory muscle weakness: supine VC, SNP, MIP (GRADE 1C)

(d) Measurement of ABG, Capillary blood gas (CBG) or transcutaneous (TcCO2) when hypercapnia is suspected by symptoms listed in PICO 2.1 (a), or when bulbar impairment precludes accurate pulmonary function testing. (GRADE 2C)

(e) Nocturnal oximetry or polygraphy when symptomatic sleep disordered breathing is suspected and other daytime indications for NIV initiation are not present. (GRADE 1C)

(f) Assessment of expiratory muscle function to include a history of weak cough, and PCF. (GRADE 1C)

Clinical remarks: It is recognized that not all sensitive measures of respiratory muscle weakness are available in all centres. The practitioners should be sensitive to the possibility of poor reliability of respiratory function testing in patients with cognitive impairment or significant bulbar dysfunction.

PICO 2.2: What criteria should be used for initiation and monitoring of non-invasive ventilation to optimize benefit?

Recommendations:

1. We recommend that practitioners offer NIV to patients with any one of the following:

(a) Orthopnea* (GRADE 1B)

(b) Daytime arterial or capillary $pCO2 > 45$ mmHg (GRADE 1B)

(c) Sleep disordered breathing as defined by oxygen saturation $< 90\%$ for $> 5\%$ of the night or $< 88\%$ for 5 consecutive minutes or a 10 mmHg increase in TcCO2 during sleep AND any of the following symptoms: dyspnea, morning headache, daytime sleepiness, or non-refreshing sleep. (GRADE 2B)

(d) FVC $< 50\%$ predicted** (GRADE 1B)

(e) FVC sitting or supine $<80\%$ predicted with symptoms as indicated in Recommendation 2.1 (a) and any other indicator of respiratory muscle involvement including SNIP $<$-50cmH2O, or MIP$<$ -65 cmH2O in males and $<$ -55 in females. (GRADE 1C)

(f) SNP $<$ -40 cmH2O or MIP $<$ -40 cmH2O** (GRADE 1C)

2. We recommend follow-up assessment of adherence and adequacy of ventilation within the first month and as indicated by symptoms and to include device download and nocturnal oxygen saturation (and TcCO2 when available). *** (GRADE 2C)

* **Clinical remark:** *Orthopnea may not be as specific for NIV initiation in individuals with significant bulbar weakness. If orthopnea is felt to be secondary to secretions in the setting of bulbar dysfunction, the secretions should be managed first.*

** **Clinical remark:** *A FVC $< 50\%$ or SNP/MIP$<$-40cmH2O have been shown to be a predictor of death at 6 months and are therefore considered to be an indication for NIV. Clinical judgement is required if there are no associated symptoms or the reliability of the values is questionable.*

*** **Clinical remark:** *The intention of device download review and monitoring of nocturnal oxygen saturation or TcCO2 (when available) is to correct leak, prevent excessive triggering (work of breathing), assure adequate volumes, prevent apneas and oxygen desaturation, and hypoventilation.*

Historically, ventilation, if it was provided to ALS patients, was delivered via tracheostomy. Since the introduction of NIV, tracheostomy ventilation is less common and thought to be a less desirable option;[78] however, rates of tracheostomy ventilation throughout the world vary widely. The highest rates are seen in Japan and other Asian countries and are reported to be 27–45% of ALS patients,[79–81] although a recent Italian study also reported a high rate of 31.3% in one region.[82] Lower rates are generally reported in American and European databases[6,7] and Canada reported a rate of 1.5% in 2010.[11]

In studies reporting tracheostomy ventilation in ALS, the proportion of patients undergoing tracheostomy after advanced care planning varies from 0% to 63.5%[78,83–89] and survival also varies. One study[84] reported a mean survival from tracheostomy of 30.3 months, while another[82] reported a survival with tracheostomy ventilation from disease onset of 47 months. One group compared survival depending on choice of intervention[79] reporting survival from disease onset as 32 months with no ventilation, 48 months with noninvasive ventilation alone and 74 months if tracheostomy ventilation was accepted. Similarly, comparing survival between different therapies, another group[15] reported a survival of 22.9 months with no ventilation, 25.8 months with NIV alone, 56.8 months if initial NIV was followed by invasive ventilation and 33.8 months if invasive ventilation alone was used. Although reporting of survival varies from time of onset of disease, from time of diagnosis or from onset of ventilation making comparison more difficult, these reports suggest that tracheostomy ventilation can prolong survival.

Although chosen in advance by some, tracheostomy may result from an acute deterioration and intubation when a personal advance directive is unavailable. Following tracheostomy for acute respiratory failure, one group[84] reported that none of the patients died in hospital; however, 70% were discharged completely ventilator dependent, and 28% partially ventilator dependent. Only one patient was liberated from mechanical ventilation. None of the patients had their tracheostomy removed. An Italian study[85] reported on 134 patients with tracheostomy ventilation over a 10-year period. This represented 10.6% of their ALS population during this period. Of those patients receiving tracheostomy ventilation, 56% were considered to be elective. A total of 20.1% died before discharge from the hospital and 48.5% were discharged home with a relatively short survival post tracheostomy. For those patients surviving the first 30 days, the median survival was 339 days from tracheostomy. They found survival dependent on age, marital status, follow-up in an ALS center, the discharge destination, and duration of disease before tracheostomy.

Bach has described decannulation after tracheostomy for acute respiratory failure in a select group of ALS patients with preserved bulbar function and the ability to generate an assisted PCF of >160 L/min.[27,90] More recently, the same authors reported successful extubation regardless of measured PCF in patients with various NMDs, although this study included few patients with ALS.[91] Despite these occasional reports and the possibility of an extended period of NIV after decannulation, tracheostomy may be required in the future as bulbar function deteriorates, and if patients choose invasive ventilation in the hope of prolonged survival.

Concern has been raised regarding the patient and caregiver satisfaction with tracheostomy. In a retrospective review of patients using tracheostomy ventilation, an older American study found that 90% of patients were happy with their decision of tracheostomy and 94% of caregivers felt this way as well.[92] A 3-year survival of 58% was reported, with a five-year survival of 33% in this series of patients. A study comparing HRQoL of both patients and caregivers supported with either tracheostomy ventilation or NIV, found a good overall HRQoL in patients, but a very high burden of care for tracheostomy ventilated caregivers, 30% of whom rated their own HRQoL lower than the patient's.[83] Vianello et al[84] reported on a cohort of 60 patients who were invasively ventilated after an episode of acute respiratory failure. Thirteen of these patients participated in an assessment of HRQoL completing the Life Satisfaction Index (LSI-11) and Beck Depression Inventory (BDI). The cumulative score on the LSI-11 was 9.3, which was similar to a group of ALS patients without tracheostomy and to that of the general population. Fifteen percent were found to be severely depressed as assessed by the BDI. Eleven of the 13 patients completing the questionnaires reported that they would choose to have a tracheostomy if they had to make the decision again. This may be a biased sample, however, given this included only 13 of their 60 patients completing the questionnaire.

In the prior publication of this guideline, the section on clearance recommended deflated or uncuffed tracheostomy tubes when possible. A recent study[89] looked at the type of tracheostomy tube required for effective ventilation in ALS. It found that 35.7% of patients with advancing bulbar dysfunction required a cuffed tube as a result of excessive air leak and hypoventilation though the majority was able to use uncuffed tubes.

Box 3. Tracheostomy Ventilation in ALS

PICO 3: Compared with NIV alone, does tracheostomy/invasive ventilation with or without preceding NIV:

1. **Prolong survival**
2. **Provide an acceptable QoL**
3. **Result in excessive caregiver burden?**

Conclusions

Tracheostomy ventilation remains an option in carefully selected patients after lengthy discussion of the implications. It is strongly preferred that these discussions occur well in advance of acute respiratory failure. Tracheostomy ventilation can prolong survival in ALS and can provide an acceptable QoL for some patients. It does, however, impose a high burden for caregivers.

Recommendations:

1. We suggest that practitioners discuss the option of tracheostomy ventilation with ALS patients. (GRADE 2B)
2. We strongly recommended that practitioners discuss this option well in advance* of acute respiratory failure. (GRADE 1C)

***Clinical Remarks:**

Tracheostomy ventilation should be discussed with patients with ALS early in the disease and reviewed during disease progression as patients may revise their wishes with symptom progression. These discussions should occur well in advance of an acute indication such as lower respiratory tract infection which may acutely worsen respiratory status. Though tracheostomy is an option, in our experience, few ALS patients choose this option given that NIV can be applied even with advancing respiratory muscle dysfunction and given that care needs with tracheostomy are likely to require institutionalization or impose a high burden for home caregivers. If tracheostomy ventilation is chosen, discussions should occur early on with patients and families to establish the conditions under which ventilation will be withdrawn (eg, If a "locked in" state occurs.)

Section 4. Respiratory muscle training in ALS

PICO 4: Does respiratory muscle training as compared to standard care improve:

1. physiologic parameters
2. survival
3. rate of progression of disease
4. time to ventilation

The role of exercise in ALS remains unclear. There has been concern that compensatory overuse of surviving muscle groups may worsen neural dysfunction and potentially accelerate the loss of motor units.[93] In contrast, other studies have suggested that exercise may be safe and effective in slowing the decline in muscle strength.[94–96] Inspiratory muscle training has been investigated in other neurological diseases such as spinal cord injury[97] and Duchenne muscular dystrophy,[98,99] but the results of these studies may not necessarily be relevant to a rapidly progressive degenerative neurological condition.

In a 2008 cohort study of ALS patients looking at a specific breathing pattern accentuating the diaphragmatic component of inspiration (Yoga breathing),[100] outcomes included QoL and FVC rate of decline. Patients served as their own controls with a 3 month run-in period measuring FVC monthly. They had difficulty in recruiting and, ultimately were able to analyze data from only 8 subjects. They found no improvement in FVC, QoL or rate of decline in FVC over 12 weeks.

A double blind RCT performed to address the question of safety and efficacy of inspiratory muscles training in ALS[101] recruited only 19 patients after screening 37 patients and looked at multiple outcomes including FVC, VC, SNIP, MIP, capillary blood gas, SF-36, ALSFRS-R and 6MWT. Although trends to improvement were seen, they found no significant difference between the groups and noted improvements in the MIP in both the training group and the control group. QoL was not impacted.

One trial looked at inspiratory muscle training (IMT) in ALS patients with early disease as defined by FVC $>$ 70% predicted, MIP $>$ 50% and an ALSFRS-R $>$24/40.[102] The trial design used a delayed intervention group as the comparator group. Group one started training at the onset of the study and group two started IMT 4 months after group one. The study lasted a total of 8 months. Their primary outcome was the ALS functional rating scale (ALSFRS) with secondary outcomes including multiple measures of respiratory function and QoL. There was no significant difference between groups in the ALSFRS or any other measure of respiratory function with the exception of the MVV, which was significantly different only at 4 months. Dyspnea was assessed using a visual analog scale and did not differ between groups. QoL showed no difference between groups using the Euro-QoL-5D questionnaire. There was also no difference in depression, fatigue or functional status, all assessed by questionnaires. In an extension of this study that included 18 patients from both groups 1 and 2, survival was measured and compared to historical controls.[103] The IMT group had a significantly longer survival from symptom onset than the historical controls: 36.99 months in the IMT group, 24.06 months in the historical controls.

Finally, the impact of expiratory strength training in ALS was studied in a delayed intervention open label trial.[104] After enrollment, there was a five week period during which no training occurred. Their primary outcome was MEP with secondary outcomes including analysis of swallowing, cough and aspiration risk. There was a significant increase in MEP and in maximal hyoid elevation after 5 weeks of treatment, but no change in cough or other parameters of the swallow assessment.

A systematic review[105] and a meta-analysis[106] have been published looking at the question of benefit of respiratory muscle training in ALS. The earlier systematic review[105] found no convincing evidence of benefit. The subsequent meta-analysis[106] looked at studies that included both ALS and Multiple Sclerosis patients. They found that MIP, MEP and FEV1 improved without change in FVC. Caution is recommended in applying this study to the ALS population given the small number of ALS patients included in the meta-analysis.

It is of note when reviewing the individual studies that the nature of the training varied from study to study in duration, intensity and training protocols. It can be noted that there did not appear to be harm associated with respiratory muscle training.

Box 4. Respiratory Muscle Training in ALS

PICO 4: Does respiratory muscle training as compared to standard care improve:

1. **physiologic parameters**
2. **survival**
3. **rate of progression of disease**
4. **time to ventilation**

Conclusions

No convincing evidence was found to support improved physiologic parameters, longer survival or slowing in rate of progression of disease using respiratory muscle training. Delay in time to ventilation was not assessed. Small numbers of patients were included in the studies.

Recommendation:

1. We do not suggest respiratory muscle training in ALS patients. (GRADE 2C)

Clinical remark:

There does not appear to be harm associated with respiratory muscle training.

Section 5. Diaphragm pacing in ALS

PICO 5: As compared to standard care, does diaphragm pacing, with or without concurrent noninvasive ventilation:

1. Prolong survival
2. Delay the time to requirement for noninvasive ventilation
3. Slow disease progression or
4. Improve QoL?

A system for diaphragm pacing, which inserted electrodes into the inferior surface of the diaphragm adjacent to the motor end points to stimulate diaphragm contraction, has been developed primarily for ventilator dependent spinal cord injured patients. It was hypothesized that stimulating intact motor units in the diaphragm of ALS patients may prevent atrophy and slow rate of decline of respiratory muscle weakness resulting in improved survival or delayed time to ventilation. A pilot trial began implanting ALS patients in 2005 and subsequent reports of this surgical cohort suggested slowing in the rate of decline of FVC which was extrapolated to improvement in survival.[107]

In 2012, 8 ALS patients paced with this pacing system were reported and compared to 354 patients that were not treated with pacing.[108] Poor tolerance was found to pacing, with 6 of their 8 patients decreasing the pacer settings and 4 of the 8 stopping pacing entirely. They also noted more rapid decline in VC and a shorter survival when compared to their cohort of ALS patients referred between 1996 and 2011.

Two RCTs of diaphragm pacing in ALS have now been reported.

The DiPALS study[109] compared NIV plus pacing (n = 37) to NIV alone (n = 37) with initiation when respiratory insufficiency was present as defined by one or more of the following: a VC 50–75% predicted, SNIP<-65cm H2O in men and -55cm H2O in women in the presence of symptoms, SNIP <-40, or pCO2 > 6kPa in the day or 6.5kPa at night or nocturnal desaturation. A total of 37 patients were enrolled in each arm. Their primary endpoint was survival from randomization to death. They also reported survival from symptom onset, QoL, compliance and adverse events. The study was terminated prematurely when the Data Monitoring and Ethics Committee noted a concerning signal in overall survival figures. They found that survival from symptom onset in the paced plus NIV group was 28 months as compared to NIV alone, which was 45 months. The patient health utility score (EQ-5D-3L) was slightly lower with pacing, although other HRQoL questionnaires were similar between the two groups. They concluded that diaphragmatic pacing should not be a routine treatment for ALS patients in respiratory failure.

The RespiStimALS study[110] enrolled patients that did not require NIV and had FVC 60–80% of predicted with evidence of diaphragm function with a phrenic stimulus. Patients meeting these criteria were randomized to receive pacing or standard care with initiation of NIV in both groups when an indication occurred. All patients had pacer insertion soon after enrollment with the control group receiving an inactive cable and sham pacing. When criteria for NIV were met, the treatment was unmasked and all patients received both pacing and NIV. NIV was initiated when FVC <50% predicted, pCO2 > 45, MIP or SNIP < 60% predicted, or nocturnal hypoxemia with 5% of recording time <90% or 5 consecutive minutes below a saturation of 88%. Decision to initiate NIV was established by an independent allocation committee. 37 patients were in each group. The study was terminated early by the study independent safety committee after becoming aware of the results of the DiPALS study and calling for a formal unplanned masked interim survival analysis which showed a mortality difference. The primary outcome was NIV free survival from randomization. They also reported survival from symptom onset, QoL and rate of decline of FVC, MIP and SNP. The median NIV free survival from randomization was 6.0 months in the early paced group and 8.8 months in the standard care group. Median survival from symptom onset in the early paced group was 51 months and this endpoint was not reached in the sham paced group. There was a more rapid decline in FVC, MIP and SNP in the early pacer group. QoL was not different between the two groups. It is interesting that the "pacer use" was higher in the sham group at the time of NIV initiation suggesting possible poor tolerance in the active pacing group. The authors concluded that there was no benefit to early pacing in terms of delay to NIV requirement or QoL and that it decreased survival.

These two RCTs both concluded that diaphragm pacing has no benefit and, in fact, may be harmful with a more rapid decline and shortened survival. The mechanism is unknown though both authors speculated on reasons for their findings. These studies are in contrast to the earlier positive reports in the surgical cohort studies. Both authors speculated that the 3 month run in period in the surgical cohort may have selected for patients with a slower disease progression, given that those with more rapid decline may have been excluded after the run-in period.

Box 5. Diaphragm pacing in ALS

PICO 5: As compared to standard care, does diaphragm pacing, with or without concurrent non-invasive ventilation:

1. **Prolong survival**
2. **Delay the time to requirement for non-invasive ventilation**
3. **Slow disease progression**
4. **Improve QoL?**

Conclusions

Despite early promising results with diaphragm pacing in ALS in a cohort of paced patients, 2 RCTs have now been reported that did not demonstrate any slowing of disease progression, or delay of time to ventilation, or improved QoL. Survival was shorter in the paced group.

Recommendation:

1. We do not recommend diaphragm pacing in patients with ALS. (GRADE 1A)

Section 6. Modes and settings

PICO 6: When applying noninvasive ventilation to ALS patients, are there specific modes or settings that improve:

1. adherence
2. patient comfort
3. gas exchange
4. survival?

In three older studies examining the benefit of NIV in ALS, both pressure and volume capable ventilators were used in the same study[22,23,71] implying that the authors considered the two modes were equivalent for the purpose of assessing benefit. Studies comparing the two modes have been reported in mixed populations.[111–114] One study[113] included both restrictive and obstructive diseases, each having different respiratory mechanics. The conclusion of these studies reporting on mixed groups was that either mode is appropriate for use in most patients. It is interesting to note that in this study, approximately one-third of the patients were bilevel "non-responders" with elevated PCO2 and reduced nocturnal saturation when treated with Bi-level. In this study, "non-responders" were returned to volume ventilation. The conclusion was that the majority of patients successfully treated with volume-cycled ventilation could also be adequately maintained on pressure controlled ventilation; however, data showed that some were less well ventilated on pressure ventilation and required a volume targeted mode. In other studies comparing the two modes of ventilation, authors report a patient preference in some. Bach proposed volume cycled ventilators in one study looking at noninvasive support in the ALS population given that the ventilator could then be used to breath stack to Maximal Inspiratory Capacity (MIC) as an aid to airway clearance.[27]

A more recent study[115] investigated whether the mode of noninvasive ventilation affected survival, gas exchange, and clinical outcomes in ALS. A French center using pressure targeted NIV was compared to a Spanish center using volume cycled NIV. The primary outcome was survival and there was no difference between centres. Symptom control appeared better with volume control NIV as well as gas exchange, time spent nocturnally with a saturation of less than 90%, mean saturation at night and minimum saturation. It is of note that the Norris Bulbar Score was significantly lower (poor bulbar function) in the pressure targeted group which may have influenced their secondary outcomes.

A study looking at tolerance of volume ventilation in ALS enrolled 87 patients who were initiated as inpatients.[116] Results showed that it was well tolerated by 92% of patients at 3 month assessment. The 8% who were intolerant were readmitted at 3 months for further habituation and remained intolerant. There was no comment on whether alternate modes were tried in the intolerant patients.

Prior studies have assessed ventilator pressure settings, including PEEP and EPAP. One evaluated the use of PEEP or end expiratory pressure in a dual limb circuit set up with a pressure targeted mode of ventilation.[117] End expiratory pressure of zero vs 4 cm was evaluated. Leaks were higher with PEEP 4 cm. They also noted increased auto-triggering and ineffective efforts with PEEP 4 cm. Decreased N3 sleep and higher sympathetic tone were also noted with the application of end expiratory pressure. On the other hand, EPAP pressure of up to 10 cm was allowed to abolish obstructions in one study, which suggested that unresolved obstructions were associated with higher mortality.[44]

A recent study compared pressure support ventilation with volume assured pressure support (VAPS) in a retrospective review of ALS patients.[118] 215 patients using pressure support were compared to 56 patients on volume assured pressure support. Both modes were well tolerated. Volume was more consistent with the volume assured group. It is likely the VAPS device was favored because the IPAP pressures in the pressure support mode were relatively low and the inspiratory times short (approximately 1 sec) and the rise times >600 msec, predisposing to smaller tidal volumes in those without a target volume.

Spontaneous timed (S/T) mode was compared to spontaneous (S) mode bilevel ventilation[119] in ALS patients and was found to improve gas exchange, respiratory events and patient ventilator synchrony when compared to the S mode.

Use of daytime mouthpiece ventilation[120] and nighttime bilevel pressure ventilation with a mask has been reported in a series of selected ALS patients. The authors defined this mode as an option in patients without significant bulbar dysfunction who require 24 hour ventilation. They noted that patients derived the greatest survival benefit if they could generate an assisted PCF > 180 L/min at initiation of mouthpiece ventilation.

Another question that remains unanswered is the optimal way to titrate NIV or to determine appropriate ventilator settings in this population. Many older studies did not describe how the ventilator settings were determined. Polysomnography to establish ventilator settings was previously rarely reported. More recently an ambulatory outpatient model of NIV initiation was described that involved an empiric daytime titration followed in 4–6 weeks by polysomnography for further titration.[75] Their comparator was an inpatient initiation model. The outpatient model showed shortened wait times for ambulatory initiation of NIV and improved survival. Other groups continue to admit patients for titrations and habituation. In the study by Martinez looking at tolerance of volume control ventilation, length of stay averaged 4.7 days for inpatient initiation of NIV.[116] Regardless of the method of initial titration, follow-up to assure adequate ventilation is suggested by 2 recent studies[43,44] reporting shortened survival with ineffective ventilation. Attention to initial titration and follow-up at 1, 3 and 6 months for evaluation and adjustment is suggested. In these studies, ventilator download with associated oximetry was used to assess adequacy of ventilation.

Box 6. Modes and Settings

PICO 6: When applying non-invasive ventilation to ALS patients, are there specific modes or settings that improve:

1. **adherence**
2. **patient comfort**
3. **gas exchange**
4. **survival?**

Conclusions

There are limited data comparing modes of NIV, settings or initiation protocols. There is a trend in many centres across the world to use pressure targeted ventilators which generally can be purchased at lower cost than ventilators providing volume control ventilation. Pressure targeted and volume targeted modes had similar survival in one recent study. Volume controlled modes, however, offered some advantages in symptom control, gas exchange and nocturnal oxygenation, but the study specifically addressing this noted a lower Norris bulbar score in the pressure targeted group which may have influenced the effectiveness of ventilation. Pressure support is often felt to be better tolerated than volume control modes, though one study showed that 92% of patients tolerated a volume control mode. When using a pressure targeted ventilator, the mode should control inspiratory time for both spontaneous and machine delivered breaths.

Both inpatient and outpatient protocols for NIV initiation have been reported and both are effective, though outpatient initiation may be preferred by patients and associated with better survival (possibly because of a shorter duration to initiation) and less cost.

Recommendations:

1. We recommend S/T mode* over S mode when delivering ventilation with pressure targeted devices. (GRADE 1C)
2. No recommendation can be made for the preferred location of the initial titration (outpatient initiation, sleep lab, or inpatient admission are all acceptable); however, delays should not be incurred irrespective of selected location. (GRADE 1C)
3. Volume-controlled ventilation is an acceptable mode and we recommend that it be used if pressure targeted modes are not tolerated or ineffective. (GRADE 1C)
4. In patients with intact bulbar function who are receiving nocturnal ventilation, we recommend use of mouthpiece ventilation rather than tracheostomy when additional daytime ventilation is required. A nasal interface may be acceptable if preferred. (GRADE 1C)

***Clinical remarks:**

Although S/T mode may improve gas exchange, respiratory events and synchrony when compared to S mode, care must be taken to assure that Ti (inspiratory time) is sufficiently long to provide adequate tidal volume and minute ventilation. In the S/T mode where the Ti is not controlled during spontaneous breaths, Ti may be too short to provide adequate tidal volume. If the percentage of triggered breaths is high, adequate support and ventilation may not be achieved. This can be resolved by use of the PC mode on ventilators that do not control Ti when the patient is triggering the device or breathing above the set rate. Other devices will control Ti on all breaths and an adequate inspiratory time may be achieved by setting a sufficiently long minimum Ti. Recommended Ti in neuromuscular patients without underlying airways disease is 1.2 to 1.5 seconds: up to a 1:1 ratio which is dependent on respiratory rate. (expert consensus)

Summary

There is increasing evidence of benefit of HMV in patients with ALS. The current guideline reviews reported benefits and seeks to advise on monitoring of respiratory status in ALS and timing of initiation of noninvasive ventilation. There is limited evidence on optimal settings and modes for patients using NIV in ALS though a timed or controlled mode is preferred. Tracheostomy remains an option for well-informed patients with ALS, but is associated with a high burden of care. Respiratory muscle training has not been shown to offer clear benefit and cannot be recommended at this time. RCTs, completed since the last publication of this guideline and addressing diaphragm pacing in ALS, have shown harm and pacing is not advised.

Much research remains to be done. Device download remotely is increasingly available and its use to improve outcomes requires further assessment. Optimal timing of NIV to optimize benefit remains an ongoing question, in particular in bulbar predominant ALS.

The intention of the CTS guideline panel for HMV is to report on changes to this guideline going forward as new evidence is published and reviewed, creating a "living document" available on the CTS website.

Implementation

The most relevant and important of the recommendations are those addressing monitoring before and after initiation of NIV and indications for initiation of noninvasive ventilation (PICO question 2).

Implementation of these recommendations

1. Wide dissemination given the variety of care providers for ALS patients

An abridged online and electronic copy "quick reference" guide with reference link to the full document will be circulated to key stakeholders involved in care of the ALS patient. This includes:

a. Directors and clinic coordinators of ALS clinics in Canada
b. The Canadian ALS Research Network (CALS) who can distribute electronically and on their platform to corresponding members, as well as introduce and present it during their quarterly meetings
c. The Canadian Association of Physical Medicine and Rehabilitation: neuromuscular Special Interest Group
d. Respirologists in Canada with membership in the Canadian Thoracic Society
e. ALS Canada with intent to distribute to provincial societies, and to make available in their online resources, accessible to clinicians, researchers and community via the ALS Canada website
f. Canadian Society of Respiratory Therapists

2. ALS clinic interaction nationally

Authors of this guideline are from across Canada and can present locally to respirologists, neurologists, physiatrists and ALS clinics. Annually, there is a national ALS Research symposium hosted by ALS Canada with participants and clinical leaders from centres across Canada. These guidelines will be presented, and a poster of the

abridged recommendations and links will be available throughout the meeting.

Every ALS Clinic in Canada has representation at the Canadian ALS Research Network, and is typically linked to their respective provincial societies, and to ALS Canada. This strong network between researchers, clinicians, community advocates and patients/families will be instrumental in ensuring broad dissemination.

Cost considerations

The aforementioned strategies are associated with minimal cost implications and maximal impact. The primary cost may be related to the purchase of equipment recommended for monitoring which is associated with a minimal initial cost outlay, but may have ongoing cost associated with disposables.

Measures of successful implementation and dissemination

As care of the individual with ALS may be by individual neurologists, physiatrists, respirologists or ALS centres, it will be challenging to monitor adoption of the guideline. The most reliable data collection at present is by ALS clinics and by the Canadian ALS research network and it is for this reason that a survey of compliance will be done through ALS clinics and the research network. At 12–24 months post publication and distribution, ALS clinics across Canada will be surveyed to assess their knowledge of and compliance with recommendations.

Current gaps and future research needs

The guideline panel identified areas where further research would improve the ability of clinicians to optimally manage patients with ALS.

1. Evaluation of device download driven setting changes (both remotely and at clinic assessments) to improve outcomes such as adherence, optimal ventilation, hospital admissions and survival.
2. Ongoing evaluation of optimal timing, in particular, in bulbar predominant patients.

Acknowledgments

The authors would like to thank Anne Van Dam from the CTS and the Chair of the CTS Canadian Respiratory Guideline Committee, Samir Gupta, for their guidance throughout the process. We would also like to acknowledge with deep appreciation our expert peer reviewers who made valuable contributions to the manuscript: Jésus Gonzalez-Bermejo, Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix, Paris, France; Noah Lechtzin, John Hopkins Hospital, Baltimore, Maryland, United States; David Leasa, London Health Sciences Centre, London, Ontario, Canada; and Jeremy Road, Vancouver General Hospital, Vancouver, British Columbia, Canada.

Editorial independence

The CTS HMV Clinical Assembly is accountable to the CTS Canadian Respiratory Guideline Committee and the CTS Board of Directors. The CTS HMV Clinical Assembly is functionally and editorially independent from any funding sources of the CTS and does not receive any direct funding from external sources. The CTS receives unrestricted grants which are combined into a central operating account to facilitate the knowledge translation activities of the CTS Clinical Assemblies. No funders played a role in the collection, review, analysis or interpretation of the scientific literature or in any decisions regarding the key messages presented in this document.

Disclosures

Members of the CTS HMV Assembly declared potential conflicts of interest at the time of appointment and these were updated throughout the process in accordance with the CTS Conflict of Interest Disclosure Policy. Individual member conflict of interest statements are posted at https://cts-sct.ca/guideline-library/.

References

1. McKim D, Road J, Avendano M, et al. Home mechanical ventilation: a Canadian thoracic society clinical practice guideline. *Can Respir*. 2011;18(4):197–215.
2. Shoesmith CL, Findlater K, Rowe A, Strong MJ. Prognosis of amyotrophic lateral sclerosis with respiratory onset. *J Neurol Neurosurg Psychiatry*. 2007;78(6):629–631.
3. Gauthier G, Verschueren A, Monnier A, Attarian S, Salort-Campana E, Pouget J. ALS with respiratory onset: clinical features and effects of non-invasive ventilation on prognosis. *Amytrophic Lateral Sclerosis*. 2010; 11:379–382.
4. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. *Brain*. 1995;18:707–719.
5. Ringel SP, Murphy JR, Alderson MK, et al. The natural history of amyotrophic lateral sclerosis. *Neurology*. 1993;43(7): 1316–1322.
6. Laub M, Midgren B. Survival of patients on home mechanical ventilation: a nationwide prospective study. *Respir Med*. 2007; 101(6):1074–1078.
7. Miller RG, Rosenberg JA, Gelinas DF; ALS practice parameters task force. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 1999;52(7):1311–1323.
8. Melo J, Homma A, Iturriaga E, Frierson L, Amato A, Anzueto A. Pulmonary evaluation and prevalence of NIV in patients with ALS: a multi-center survey and proposal of a pulmonary protocol. *J Neurol Sci*. 1999;169(1–2):114–117.
9. Bradley WG, Anderson F, Bromberg M, Gurmann L, Harati Y, Ross M. Current management of ALS: comparison of the ALS CARE database and the AAN Practice Parameter. The

American Academy of Neurology. *Neurology*. 2001;57(3):500–504.
10. Jackson CE, Lovitt S, Gowda N, Anderson F, Miller RG. Factors correlated with NPPV use in ALS. *Amyotrophic Lateral Sclerosis*. 2006;7(2):80–85.
11. Ritsma BR, Berger MJ, Charland DA. NIPPV: prevalence, approach and barriers to use at Canadian ALS centres. *Can J Neurol Sci*. 2010;37(1):54–60.
12. O'Neill CL, Williams TL, Peel ET, McDermott CJ, Shaw PJ, Gibson GJ. Non-invasive ventilation in motor neuron disease: an update of current UK practice. *J Neurol Neurosurg Psychiatry*. 2012;83(4):371–376.
13. Berlowitz DJ, Howard ME, Fiore JF, Jr, et al. Identifying who will benefit from non-invasive ventilation in amyotrophic lateral sclerosis/motor neurone disease in a clinical cohort. *J Neurol Neurosurg Psychiatry*. 2016;87(3):280–286.
14. Hirose T, Kimura F, Hiroki T, et al. Clinical characteristics of long-term survival with non-invasive ventilation and factors affecting the transition to invasive ventilation in ALS. Muscle and Nerve 2018 April 20 (Epub doi:10.1002/mus.26149)
15. Dreyer P, Lorenzen CK, Schou L, Felding M. Survival in ALS with home mechanical ventilation non-invasively and invasively: a 15-year cohort study in west Denmark. *Amyotrophic Lateral Scler Frontotemporal Degener*. 2014;15(1–2):62–67.
16. Brouwers M, Kho ME, Browman GP. for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *CMAJ*. 2010;182(18):E829–E842.
17. Guyatt G, Gutterman D, Baumann MH. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129(1):174–181.
18. Gupta S, Rai N, Bhattacharrya O. Optimizing the language and format of guidelines to improve guideline uptake. *CMAJ*. 2016;188(14):E362–E368.
19. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of noninvasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. *Lancet Neurology*. 2006;5(2):140–147.
20. Radunovic A, Annane D, Rafiq MK, Brassington R, Mustafa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database of Systematic Reviews*. 2017;CD004427.
21. Pinto AC, Evangelista T, Carvalho M, Alves MA, Sales Luis ML. Respiratory assistance with a noninvasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. *J Neurol Sci*. 1995;129(suppl):19–26.
22. Aboussouan LS, Khan SU, Meeker DP, Stelmach K, Mitsumoto H. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. *Ann Intern Med*. 1997;127(6):450–453.
23. Aboussouan LS, Khan SU, Banerjee M, Arroliga AC, Mitsumoto H. Objective measures of the efficacy of noninvasive positive pressure ventilation in amyotrophic lateral sclerosis. *Muscle Nerve*. 2001;24(3):403–409.
24. Sancho J, Martínez D, Bures E, Díaz JL, Ponz A, Servera E. Bulbar impairment score and survival of stable amyotrophic lateral sclerosis patients after noninvasive ventilation initiation. *ERJ Open Res*. 2018;4(2):00159–2017.
25. Berlowitz DJ, Detering K, Schachter L. A retrospective analysis of sleep quality and survival with domiciliary ventilator support in motor neuron disease. *Amyothroph Lateral Scler*. 2006;7(2):100–106.
26. Kleopa KA, Sherman M, Neal B, Romano GJ, Heiman-Patterson T. Bilevel improves survival and rate of pulmonary function decline in patients with ALS. *J Neurol Sci*. 1999;164(1):82–88.
27. Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory AIDS. *Chest*. 2002;122(1):92–98.
28. Lo Coco D, Marchese S, Pesco MC, La Bella V, Piccoli F, Lo Coco A. Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. *Neurology*. 2006;67(5):761.
29. Pinto A, de Carvalho M, Evangelista T, Lopes A, Sales LL. Nocturnal pulse oximetry: a new approach to establish the appropriate time for noninvasive ventilation in ALS patients. *Amyotroph Lateral Scler Other Motor Neuron Disorders*. 2003;4:31–35.
30. Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ. Noninvasive ventilation in ALS: indications and effect on quality of life. *Neurology*. 2003;61(2):171–177.
31. Newsom-Davis IC, Lyall RA, Leigh PN, Moxham J, Goldstein LH. The effect of noninvasive positive pressure ventilation on cognitive function in amyotrophic lateral sclerosis (ALS): a prospective study. *J Neurol Neurosurg Psychiatry*. 2001;71(4):482–487.
32. Lyall RA, Donaldson N, Fleming T, et al. A prospective study of quality of life in ALS patients treated with noninvasive ventilation. *Neurology*. 2001;57(1):153–156.
33. Jackson CE, Rosenfeld J, Moore DH, et al. A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients. *J Neurol Sci*. 2001;191(1-2):75–78.
34. David WS, Bundlie SR, Mahdavi Z. Polysomnographic studies in amyotrophic lateral sclerosis. *J Neuro Sci*. 1997;152(Suppl):S29–S35.
35. Hazenberg A, Kerstjens HAM, Prins SCL, Vermeulen KM, Wijkstra PJ. Is chronic ventilatory support really effective in patients with amyotrophic lateral sclerosis? *J Neurol*. 2016;263(12):2456–2461.
36. Vandoorne E, Vrijsen B, Belge C, Testelmans D, Buyse B. Noninvasive ventilation in amyotrophic lateral sclerosis: effects on sleep quality and quality of life. *Acta Clin Belg*. 2016;71(6):389–394.
37. Gay PC, Westbrook PR, Daube JR, Litchy WJ, Windebank AJ, Iverson R. Effects of alterations in pulmonary function and sleep variables on survival in patients with amyotrophic lateral sclerosis. *Mayo Clin Proc*. 1991;66(7):686–694.
38. Ferguson KA, Strong MJ, Ahmad D, George CFP. Sleep disordered breathing in amyotrophic lateral sclerosis. *Chest*. 1996;110(3):664–669.
39. Kimura K, Tachibana N, Kimura J, Shibasadi H. Sleep-disordered breathing at an early stage of amyotrophic lateral sclerosis. *J Neurol Sci*. 1999;164(1):37–43.
40. Arnulf I, Similowski T, Salachas F, et al. Sleep disorders and diaphragm function in patients with amyotrophic lateral sclerosis. *Am J Respir Crit Care Med*. 2000;161(3):849–856.
41. Atalaia A, Carvalho MD, Evangelista T, Pinto A. Sleep characteristics of amyotrophic lateral sclerosis in patients with preserved diaphramgmatic function. *Amyotroophic Lateral Sclerosis*. 2007;8(2):101–105.
42. Katzberg HD, Selegiman A, Guion L, et al. Effects of noninvasive ventilation on sleep outcomes in amyotrophic lateral sclerosis. *J Clin Sleep Med*. 2013;9(4):345–351.
43. Gonzalez-Bermejo J, Morelot-Panzini C, Arnol N, et al. Prognostic value of efficiently correcting nocturnal desaturations after one month of non-invasive ventilation in amyotrophic lateral sclerosis: a retrospective moncentre observational cohort study. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14(5-6):373–379.
44. Georges M, Attali V, Golmard JL, et al. Ventilation. *J Neurol Neurosurg Psychiatry*. 2016;87(10):1045–1050.
45. Vrijsen B, Buyse B, Belge C, et al. Noninvasive ventilation improves sleep in amyotrophic lateral sclerosis: a prospective polysomnographic study. *J Clin Sleep Med*. 2015;11(5):559–566.
46. Vrijsen B, Testelmans D, Belge C, Vanpee G, Van Damme P, Buyse B. Patient-ventilator asynchrony, leaks and sleep in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2016;17(5–6):343–350.

47. Fallat RJ, Jewitt B, Bass M, Kamm B, Norris FH. Spirometry in amyotrophic lateral sclerosis. *Arch Neurol*. 1979;36(2):74–80.
48. Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology*. 1998;50(1):66–72.
49. Lyall FA, Donaldson N, Polkey MI, Leigh PN, Moxham J. Respiratory muscle strength and ventilator failure in amyotrophic lateral sclerosis. *Brain*. 2001;124(10):2000–2013.
50. Zavorsky GS, Cao J, Mayo NE, Gabbay R, Murias JM. Arterial versus capillary blood gases: a meta-analysis. *Respir Physiol Neurobiol*. 2007;155(3):268–279.
51. van Oppen JD, Daniel PS, Sovani MP. What is the potential role of transcutaneous carbon dioxide in guiding acute noninvasive ventilation? *Respir Care*. 2015;60(4):484–491.
52. Storre JH, Magnet FS, Dreher M, Windisch W. Transcutaneous monitoring as a replacement for arterial pCO2 monitoring during nocturnal non-invasive ventilation. *Respiratory Medicine*. 2011;105(1):143–150.
53. Polkey MI, Lyall RA, Yang K, Johnson E, Leigh PN, Moxham J. Respiratory muscle strength as a predictive biomarker for survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med*. 2017;195(1):86–95.
54. Morgan RK, McNally S, Alexander M, Conroy R, Hardiman O, Costello RW. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med*. 2005;171(3):269–274.
55. Fitting JW, Paillex R, Hirt L, Aebischer P, Schluep M. Sniff nasal pressure: a sensitive respiratory test to assess progression of amyotrophic lateral sclerosis. *Ann Neurol*. 1999;46(6):887–893.
56. Capozzo R, Quaranta VN, Pellegrini F, et al. Sniff nasal inspiratory pressure as a prognostic factor of tracheostomy or death in amyotrophic lateral sclerosis. *J Neurol*. 2015;262(3):593–603.
57. Enache I, Pistea C, Fleury M, et al. Ability of pulmonary function decline to predict death in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(7–8):511–518.
58. Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry*. 2005;77(3):390–392.
59. Prell T, Ringer TM, Wullenkord K, et al. Assessment of pulmonary function in amyotrophic lateral sclerosis: when can polygraphy help evaluate the need for non-invasive ventilation? *J Neurol Neurosurg Psychiatry*. 2016;87(9):1022–1026.
60. Bye PT, Ellis ER, Issa FG, Donnelly PM, Sullivan CE. Respiratory failure and sleep in neuromuscular disease. *Thorax*. 1990;45(4):241–247.
61. Varrato J, Siderowf A, Damiano P, Gregory S, Feinberg D, McCluskey L. Postural change of forced vital capacity predicts some respiratory symptoms in ALS. *Neurology*. 2001;57(2):357–359.
62. Baumann F, Henderson RD, Morrison SC, et al. Use of respiratory function tests to predict survival in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2010;11(1-2):194–202.
63. Just N, Bautin N, Danel-Brunaud V, Debroucker V, Matran R, Perez T. The Borg dyspnoea score: a relevant clinical marker of inspiratory muscle weakness in amyotrophic lateral sclerosis. *Eur Respir J*. 2010;35(2):353–360.
64. Andrews JA, Meng L, Kulke SF, et al. Association between decline in slow vital capacity and respiratory insufficiency, use of assisted ventilation, tracheostomy, or deat in patients with amyotrophic lateral sclerosis. *JAMA Neurology*. 2018;75(1):59–64.
65. Liberty Jenkins JA, Sakamuri S, Katz JS, et al. Phrenic nerve conduction studies as a biomarker of respiratory insufficiency in amyotrophic lateral sclerosis. *Amyotroph Later Scler Frontotemporal Degener*. 2016;17(3–4):213–220.
66. Pinto S, Pinto A, de Carvalho M. Phrenic nerve studies predict survival in amyotrophic lateral sclerosis. *Clin Neurophysiol*. 2012;123(12):2454–2459.
67. Hiwatani Y, Mayumi S, Miwa H. Ultrasonography of the diaphragm in amyotrophic lateral sclerosis: clinical significance in assessment of respiratory functions. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14(2):127–131.
68. Pinto S, Alves P, Pimentel B, Swash M, de Carvalho M. Ultrasound for assessment of diaphragm in ALS. *Clin Neurophysiol*. 2016;127(1):892–897.
69. Vender RL, Mauger D, Walsh S, Alam S, Simmons Z. Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis on survival. *Amyotroph Lateral Scler*. 2007;8(1):36–41.
70. Lechtzin N, Cudkowicz ME, De Carvalho M, et al. Respiratory measures in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2018;19(5–6):1–10.
71. Ferraro E, Prats E, Povedano M, Marinez-Matos Manresa F, Escarrabill J. Survival in ALS with home mechanical ventilation. The impact of systematic respiratory assessment and bulbar involvement. *Chest*. 2005;127:2132–2138.
72. Lechtizin N, Scott Y, Busse AM, Clawson LL, Kimball R, Wiener CM. Early use of noninvasive ventilation prolongs survival in subjects with ALS. *Amyotroph Lateral Scler*. 2007;8:185–188.
73. Jacobs TL, Brown DL, Jonggyu B, Migda EM, Funckes T, Gruis KL. Trial of early noninvasive ventilation for ALS: a pilot placebo-controlled study. *Neurology*. 2016;87(18):1878–1883.
74. Vandenberghe N, Vallet A-E, Petitjean T, et al. Absence of airway secretion accumulation predicts tolerance of noninvasive ventilation in subjects with amyotrophic lateral sclerosis. *Respiratory Care*. 2013;58(9):1424–1432.
75. Sheers N, Berlowitz DJ, Rautela L, Batchelder I, Hopkinson K, Howard ME. Improved survival with an ambulatory model of non-invasive ventilation implementation in motor neuron disease. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15(3–4):180–184.
76. Gonzalez Calzada N, Soro EP, Gomez LM, et al. Factors predicting survival in amyotrophic lateral sclerosis patients on non-invasive ventilation. *Amyotroph Lateral Scler Frontotemporal Degener*. 2016;17(5–6):337–342.
77. Devine MS, Ballard E, O'Rourke P, Kiernan MC, Mccombe PA, Henderson RD. Targeted assessment of lower motor neuron burden is associated with survival in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2016;17(3–4):184–190.
78. Cazzoli PA, Oppenheimer EA. Home mechanical ventilation for amyotrophic lateral sclerosis: nasal compared to tracheostomy-intermittent positive pressure ventilation. *J Neurol Sc*. 1996;139(Suppl):123–128.
79. Tagami M, Kimura F, Nakajima H, et al. Tracheostomy and invasive ventilation in Japanese ALS patients: decision-making and survival analysis: 1990–2010. *J Neurolog Sci*. 2014;344(1–2):158–164.
80. Lee CT-C, Chiu Y-W, Wang K-C, et al. Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in Taiwan. *J Epidemiol*. 2013;23(1):35–40.
81. Bae JS, Hong Y-H, Baek W, et al. Current status of the diagnosis and management of amyotrophic lateral sclerosis in Korea: a multi-center cross-sectional study. *J Clin Neurol*. 2012;8(4):293–300.
82. Spataro R, Bono V, Marchese S, La Bella V. Tracheostomy mechanical ventilation in patients with ALS: clinical features and survival analysis. *J Neurol Sci*. 2012;323(1–2):66–70.
83. Kaub-Wittemer D, von Steinbuchel N, Wasner M, Laier-Groeneveld G, Burasio GD. Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers. *J Pain Symptom Manag*. 2003;26(4):890–896.

84. Vianello A, Arcaro G, Palmieri A, et al. Survival and quality of life after tracheostomy for acute respiratory failure in patients with amyotrophic lateral sclerosis. *J Crit Care*. 2011;26: 329e7–32914.
85. Chio A, Calvo A, Ghiglione P, Mazzini L, Mutani R, Mora G. Tracheostomy in ALS: a 10 year population-based study in Italy. *J Neurol Neurosurg Psychiatry*. 2010;81(10):1141–1143.
86. Moss AH, Oppenheimer EA, Casey P, et al. Patients with amyotrophic lateral sclerosis receiving long-term mechanical ventilation. Advance care planning and outcomes. *Chest*. 1996; 110(1):249–255.
87. Hirano YM, Yamazaki Y, Shimizu J, Toagari T, Bryce TJ. Ventilator dependence and expressions of need: a study of patients with amyotrophic lateral sclerosis in Japan. *Soc Sci Med*. 2006;62(6):1403–1413.
88. Sancho J, Servera E, Diaz JL, Banuls P, Marin J. Home tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: causes, complications and 1-year survival. *Thorax*. 2011;66(11):948–952.
89. Sancho J, Servera E, Bañuls P, Marín J. Prolonging survival in amyotrophic lateral sclerosis: efficacy of noninvasive ventilation and uncuffed tracheostomy tubes. *Am J Phys Med Rehabil*. 2010;89(5):407–411.
90. Bach JR, Goncalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness: a new management paradigm. *Chest*. 2010;137(5):1033–1039.
91. Bach JR, Sinquee DM, Saporito LR, Botticello A. Efficacy of mechanical insufflation-exsufflation in extubating unweanable subjects with restrictive pulmonary disorders. *Respir Care*. 2015; 60(4):477–483.
92. Oppenheimer EA. Amyotrophic lateral sclerosis: care, survival and QoL on home mechanical ventilation. In: Robert D, Make BJ, Leger P eds. *Home Mechanical Ventilation*. Paris, Arnette Blackwell. 1995:249–260.
93. Vucic S, Krishnan AV, Kiernan MC. Fatigue and activity dependent changes in axonal excitability in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2007;78(11):1202–1208.
94. Drory VE, Goltsman E, Reznik JG, Mosek A, Korczyn AD. The value of muscle exercise in patients with amyotrophic lateral sclerosis. *J Neurol Sci*. 2001;191(1–2):133–137.
95. Bello-Haas VD, Florence JM, Kloos AD, et al. A randomized controller trail of resistance exercise in individuals with ALS. *Neurology*. 2007;68(23):2003–2007.
96. Pinto AC, Alves M, Nogueira A, et al. Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise? *J Neurol Sci*. 1999;169(1–2):69–75.
97. Tamplin J, Berlowitz DJ. A systematic review and meta-analysis of the effects of respiratory muscle training on pulmonary function in tetraplegia. *Spinal Cord*. 2014;52(3):175–180.
98. Rodillo E, Noble-Jamieson CM, Aber V, Heckmatt JZ, Muntoni F, Dubowitz V. Respiratory muscle training in Duchenne Muscular Dystrophy. *Arch Dis Child*. 1989;64(5):736–738.
99. Winkler G, Zifko U, Nader A, et al. Dose-dependent effects of inspiratory muscle training in neuromuscular disorders. *Muscle Nerve*. 2000;23(8):1257–1260.
100. Nardin R, O'donnell C, Loring SH, et al. Diaphragm training in amyotrophic lateral sclerosis. *J Clin Neuromuscular Disease*. 2008;10(2):56–60.
101. Cheah BC, Boland RA, Brodaty NE, et al. INSPIRATIonAL – INSPIRAtory muscle training in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2009;10(5-6):384–392.
102. Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2012; 13(1):33–43.
103. Pinto S, de Carvalho M. Can inspiratory muscle training increase survival in early-affected amyotrophic lateral sclerosis patients? *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14(2):124–126.
104. Plowman EK, Watts SA, Tabor L, et al. Impact of expiratory strength training in amyotrophic lateral sclerosis. *Muscle Nerve*. 2016;54(1):48–53.
105. Eidenberger M, Nowotny S. Inspiratory muscle training in patients with amyotrophic lateral sclerosis: a systematic review. *NeuroRehabilitation*. 2014;35:349–361.
106. Ferreira GD, Costa ACC, Plentz RDM, Coronel CC, Sbruzzi G. Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis. *Phsiotherpay*. 2016;102(3):221–228.
107. Onders RP, Elmo MJ, Kaplan C, Katirji B, Schilz R. Final analysis of the pilot trial of diaphragm pacing in amyotrophic lateral sclerosis with long-term follow up: daphragm pacing positiviely affects diaphragm respiration. *Am J Surg*. 2014; 207(3):393–397.
108. Mahajan KR, Bach JR, Saporito L, Perez N. Diaphragm pacing and noninvasive respiratory management of amyotrophic lateral sclerosis/motor neuron disease. *Muscle Nerve*. 2012;46:851–855.
109. DiPALS Writing Committee; DiPALS Study Group Collaborators. Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicentre. Open-Label, Randomized Controlled Trial. *Lancet Neurol*. 2015;14:883–892.
110. Gonzalez-Bermejo J, Morelot-Panzini C, Tanguy M-L, et al. Early diaphragm pacing in patients with amyotrophic lateral sclerosis (RespiStimALS): a randomised controlled triple-blind trial. *Lancet Neurology*. 2016;15(12):1217–1227.
111. Restrick LJ, Fox NC, Braid G, Ward EM, Paul EA, Wedzicha JA. Comparison of nasal pressure support ventilation with nasal intermittent positive pressure ventilation in patients with nocturnal hypoventilation. *Eur Respir J*. 1993;6(3):364–370.
112. Meecham Jones DJ, Wedzicha JA. Comparison of pressure and volume preset nasal ventilator systems in stable chronic respiratory failure. *Eur Respir J*. 1993;6(7):1060–1064.
113. Schonhofer B, Sonneborn M, Haidl P, Bohrer H, Kohler D. Comparison of two different modes for noninvasive mechanical ventilation in chronic respiratory failure: volume versus pressure controlled device. *Eur Respir J*. 1997;10(1):184–191.
114. Chadda K, Clair B, Orlikowski D, Macadoux G, Raphael JC, Lofaso F. Pressure support versus assisted controlled noninvasive ventilation in neuromuscular disease. *Neuocrit Care*. 2004; 1(4):429–434.
115. Sancho J, Servera E, Morelot-Panzini C, Salachas F, Similowski T, Gonzalez-Bermejo J. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15(1–2): 55–61.
116. Martinez D, Sancho J, Servera E, Marin J. Tolerance of volume control noninvasive ventilation in sujects with amyotrophic lateral sclerosis. *Respiratory Care*. 2015;60(12):1765–1771.
117. Crescimanno G, Greco F, Arrisicato S, Morana N, Marrone O. Effects of positive end expiratory pressure administration during non-invasive ventilation in patients affected by amyotrophic lateral sclerosis: a randomized crossover study. *Respirology*. 2016;21(7):1307–1313.
118. Nicholson TT, Smith SB, Siddique T, et al. Respiratory pattern and tidal volumes differ in pressure support and volume-assured pressure support in Amyotrophic Lateral Sclerosis. *Annals ATS*. 2017;14(7):1139–1146.
119. Vrijsen B, Buyse B, Belge C, Vanpee G, Van Damme P, Testelmans D. Randomized cross-over trial of ventilator modes during non-invasive ventilation titration in amyotrophic lateral sclerosis. *Respirology*. 2017;22(6):1212–1218.
120. Bedard M-E, McKim DA. Daytime mouthpiece for continuous noninvasive ventilation in individuals with amyotrophic lateral sclerosis. *Respir Care*. 2016; 61(10):1341–1347.

Appendix 1. Search strategy: HMV for patients with ALS guideline update

Study types	Any. To be as inclusive as possible. Guidelines, meta-analysis, systematic review, randomized controlled trial, cohort study, case control study, case series, or case report
Data sources	MEDLINE® (OVID); Embase® (OVID); HealthStar®; Cochrane Library®, Canadian Medical Association InfoBase®; and the National Guideline Clearinghouse®
Search terms	Neuromuscular Diseases, Respiratory Insufficiency, respiratory insufficiency mp., respiratory failure, respiratory failure.mp., breathing failure.mp., breathing difficult*.mp., respiratory muscle weakness.mp., ("pulmonary function" and failure) mp., Respiration Disorders, Respiration, Hypercapnia, pulmonary disease.mp., amyotrophic lateral sclerosis.mp., Amyotrophic Lateral Sclerosis, ALS.mp., artificial ventilation/ or ventilator/ or ventilated patient/ or Oxygen therapy/ or assisted ventilation/ or Ventilators, Mechanical/ or Ventilation/ or Ventilators, Negative Pressure/ or ventilators negative pressure.mp. or ventil.ti. or mechanical ventilation.mp. or Positive-Pressure Respiration, Intrinsic/ or Intermittent Positive Pressure Ventilation/ or Pulmonary Ventilation/ or positive-pressure respiration.mp. or Positive-Pressure Respiration/ or NIV.mp. or NIPPV.mp. or VAC.mp. or Respiration, Artificial, exp *respiratory failure, ((respiratory or breathing) adj (failure or insufficiency or difficult*)).tw., breathing muscle/ and muscle weakness, respiratory muscle weakness.tw., ("pulmonary function" and failure).mp., breathing disorder, hypercapnia, ALS.tw.,respiratory muscle training, inspiratory muscle training, diaphragm pacing, phrenic pacing, tracheostomy ventilation, tracheostomy
Language criteria	All publications in English were reviewed and considered for inclusion.
First literature search	2010 to September 30, 2017
Results	153 abstracts citing ALS on the literature reviews: **Inclusion:** 47 abstracts **Exclusion:** 106 abstracts ***Reasons for exclusion:*** • 62 not addressing the PICO questions • 32 abstracts or letters • 5 review articles • 6 duplicates • 1 foreign language ***Excluded after full review:*** • 3 not PICO relevant • 2 review articles
Second literature search	October 1, 2017 to March 31, 2018
Results	26 abstracts citing ALS on the literature reviews: **Inclusion:** 4 abstracts **Exclusion:** 22 exclusions ***Reasons for exclusion:*** • 10 not PICO relevant • 4 letters • 1 Foreign language • 4 reviews • 2 abstracts • 1 editorial
Target users	Health care teams that care for individuals who are at risk for or require ventilatory assistance. Respirologists, physiatrists, neurologists, family practitioners, nurses, respiratory therapists, physiotherapists, and other health care professionals can use this guideline to help inform their clinical practice with regard to HMV. This guideline is also intended for use by ventilator-assisted individuals (VAIs) and their caregivers to help them make informed decisions on home mechanical ventilation and by health care decision makers to aid in establishing policy and making funding decisions
Scope of this guideline	• To address the benefits of mechanical ventilation in ALS, respiratory muscle testing, and monitoring required, timing of initiation of ventilation and modes, settings, and place of initiation • To review diaphragm pacing and respiratory muscle training • To address tracheostomy ventilation