Management of Respiratory Insufficiency in MND/ALS Patients: An Evidence Based Review.

Objective:

This systematic review comprises of an objective appraisal of the evidence in regard to the management of respiratory insufficiency for patients with motor neurone disease (MND), in particular amyotrophic lateral sclerosis (ALS). The primary aim is to establish evidence-based and patient and carer centred guidelines, with secondary aims of generating new research questions to be addressed in future studies and identifying areas where further research is needed.

Justification:

Respiration requires the normal function of three muscle groups: the muscles of inspiration, the muscles involved in expiration and the muscles that control the upper airway. As motor neurone disease progresses in a patient, a weakness or impairment of the inspiratory and expiratory muscles will develop. Inspiratory muscle weakness has been identified as the primary determinant of ventilatory failure and respiratory symptoms (Polkey et al, 1998). Expiratory muscle strength does not appear to affect ventilation directly but does result in the loss of cough or inability to clear secretions from the lungs, thus leading to a higher risk of atelectasis and lower respiratory tract infections (Sherman & Paz, 1994). The weakening of respiratory muscles is a significant indicator of survival and a progressive worsening of respiratory muscle weakness can lead to respiratory insufficiency and a diminished quality of life (Bourke et al, 2001). Such morbidity includes difficulties in breathing, morning headaches, weak cough, aspiration, breathing disturbances during sleep, chronic nocturnal hypoventilation, and chest infections. Most patients with MND/ALS will develop symptoms of respiratory insufficiency during the course of their disease and respiratory failure is frequently an urgent medical problem either as a first symptom or later in the course of the disease (Bromberg et al, 1996). Respiratory failure is also responsible for the majority of deaths from MND/ALS (Borasio, Gelinas & Yanagisawa, 1998).

Since systems of respiratory insufficiency compromise the quality of life of MND/ALS patients, clinical management is necessary. In practice, the clinical management of MND/ALS patients in Europe tends to be largely based on clinical experience and on 'expert opinions' (Borasio et al, 2001). Surveys on standards of care for the management of respiratory failure in MND/ALS patients report varying levels of provision of care in western countries. Borasio et al (2000) in their survey on standards of clinical management of palliative care for MND/ALS patients in Europe found that 43% of centres regularly checked respiratory function using FVC, 90% routinely discussed respiratory issues. Bourke et al (2002) also found a high level of activity of neurologists in the management of respiratory insufficiency in MND/ALS patients in Britain but found that a proportion of the respondents did not assess vital capacity or other indices of respiratory function in the routine assessment of MND/ALS patients (this percentage was not reported). Melo et al (1999) found that out of 48 multidisciplinary ALS centres in the USA, 17 to 20 centres had performed pulmonary function tests. Sixteen centres used signs of hypoventilation and worsening forced vital capacity as indicators for non-invasive ventilation and only four had established protocols (Melo et al, 1999). While these prevalence surveys show the operation of clinical management of respiratory insufficiency, they point to the need for a specific procedure for monitoring and managing respiratory insufficiency in motor neurone disease. Such a situation should be rectified with the production of guidelines, based on the best evidence available for the clinical management of respiratory insufficiency in MND/ALS patients. Miller et al (1999) addressed the management of respiratory care as part of their evidence-based review on the provision of care for patients with amyotrophic lateral sclerosis. From this, they suggested some guidelines or parameters. However the issue of respiratory management warrants a more detailed systematic review of methods and recommendations. Moreover, it has been some years since the publication of Miller et al (1999) so it is appropriate to update their proposed guidelines and to tailor them to the needs of the UK population. On this basis, a list of review questions were developed pertaining to the management of dyspnoea and mechanical ventilation (See Table 1). These questions are viewed to be central to the management of respiratory insufficiency in MND/ALS patients.

Table 1.
List of Review Questions.

Management of Respiratory Insufficiency.
i. How can we best detect early respiratory insufficiency?
ii. What are the recommended procedures for monitoring respiratory function?
iii. How can respiratory insufficiency be managed?
iv. What are the patients' and carers' views on managing difficulties with respiratory function?
v. Can non-invasive ventilation help respiratory insufficiency in MND/ALS?
vi. Can invasive ventilation help respiratory insufficiency in MND/ALS?
vii. What is the optimal method of withdrawing both non-invasive and invasive ventilation from patients with MND/ALS?

Review Methods:

Studies were identified through computerized searches of 32 databases, including MEDLINE, CINAHL, PsychINFO, Cochrane Controlled Trials Register, National Research Register and Conference Papers Index. Internet searches of websites of drug companies and MND/ALS research web sites, 'snow balling' and hand searches were also employed to locate any unpublished study or other 'grey literature' on respiration and MND/ALS. Since management of MND/ALS involves a number of health professionals and care workers, searches were made across multiple disciplines. No time frame was imposed on the search so that the articles would include everything ever published on MND/ALS and respiration. This provided large catchments of literature, which increased probability of identifying all relevant studies. On initial screening of titles and abstracts, a large number of duplicates (including articles printed in different languages and journals) were found but once these were identified and irrelevant articles deleted, a total of 496 articles were recorded.

According to the protocol, only articles pertaining to the management of respiratory insufficiency in MND/ALS patients can be included (See Table 2 for study selection criteria). Opinions expressed in letters to editors on published studies were also removed from the systematic review, as these did not reveal any inconsistencies with the data that the systematic review had not already detected nor did they include primary research of the writer. Single case reports were also omitted, as these were descriptive and did not mention best practice in management issues. In addition, they cannot be generalised to the average patient. All other managerial issues pertaining to MND/ALS, general and descriptive articles on MND/ALS (including descriptions of the respiratory system), experiments on animal populations and the management of respiratory insufficiency in other populations were excluded. Studies that fulfilled the inclusion criteria were retrieved from more detailed evaluation and the quality of the studies were assessed on the basis of methodology, bias, internal and external validity. A taxonomy of studies was adhered to, based on the proposed hierarchy of studies by the US Department of Health and Human

Table 2
Study Selection Criteria

Selection Criteria	Inclusion Criteria	Exclusion Criteria
Population	MND/ALS patients in general.	All other patients, animals and humans
Interventions	Clinical management of respiration	All other clinical management issues pertaining to MND/ALS.
Outcomes	(1) Management of respiratory insufficiency (2) Ease of discomfort for patient (3) Assessment of need for ventilatory support (4) Adverse or positive effects of non-invasive and invasive interventions	All other outcomes
Study Design	(1) randomised controlled trials (2) non-randomised/quasi-experimental trials (3) observational studies (4) expert opinion	(1) single cases (2) letters of opinion (3) expert opinion if not backed by a narrative review (4) descriptions of the respiratory system.

Services (1993) and the quality of evidence was assessed using a modified version of a system suggested by the Oxford Centre for Evidence-based Medicine (http:///www.cebm.net) (see Table 3). The minimum quality threshold for the selection of studies was set at grade 5, i.e. expert opinion, which is supported by a narrative review and published in peer-reviewed journals. Such a low threshold was chosen due to the lack of grade 1 evidence. However, grade 5 evidence was only utilised in this review where there was a dearth of higher quality studies on a particular topic or question. The study selection process reduced the number of 496 down to 123 articles for data synthesis.

All studies selected addressed management of respiratory insufficiency in MND/ALS patients, though some were geared towards neuromuscular patients in general but had mentioned MND/ALS patients or addressed the management of ALS disease. The majority of studies were observational studies and were largely grade 4 (case-series). There were no randomised controlled trials, although there were two systematic reviews of observational studies - Miller et al (1999) on management of MND/ALS and Ginsberg & Lowe (2002) on cost effectiveness of treatments for MND/ALS - thus setting the highest grade of evidence as 2a. Two surveys and one descriptive article on current practices of respiratory care in Europe were included as background information for the ensuing review questions (Bourke et al, 2002; Borasio et al, 2001; Borasio et al, 1998). It is worth noting that when reviewing the best evidence for effectiveness of a clinical managerial issue, observational studies, despite their vulnerability to selection bias, are beneficial to identifying adverse effects of treatments and measuring quality of service delivery and management. Due to the variation in sample characteristics, study design and statistical tests used, it was deemed more suitable to report the results qualitatively rather than attempt to quantify the results. A minimum number of patients and defined patient characteristics per observational or controlled quasi-experimental study were not set as criteria for inclusion. Firstly, the MND/ALS sub-population in the general population is small so sample sizes will also be small. Secondly, the ALS population varies in demographics and disease severity, so compilation of all studies can help to identify the common issues of respiration. In regards to the development of the guidelines, each guideline will be classified in accordance to the strength of recommendation (see Table 4). Class A studies encompass systematic reviews with meta analysis or randomised controlled trials, Class B studies are experimental studies, Class C observational studies and Class D refers to expert opinion. Since all the guidelines comprised of either grade 2 or grade 3 evidence, this makes them more recommendations than guidelines.

Table 3.
Study Hierarchy for the Clinical Management of Respiratory insufficiency; Grading of Quality of Evidence for the Individual Studies

Study Hierarchy for the Clinical Management of Respiratory insufficiency:

1 Systematic reviews and meta-analysis.
2 Randomised controlled trials.
3 Non-randomised controlled trials (also known as quasi-experimental studies).
4 Observational studies with comparison group (analytical) – cohort studies, case control studies.
5 Observational studies without comparison groups (descriptive) – cross-sectional studies (prevalence), before-and-after studies, case series, surveillance.
6 Expert opinion based on pathophysiology, bench research or consensus.

Grading of Quality of Evidence for the Individual Studies:

1a Systematic review with homogeneity of RCTs – worrisome heterogeneity to be tagged with a "-".

1b Individual RCT with a narrow confidence interval

1c Quasi-experimental/ RCT where all patients died before Rx became available but some now survive on it; or when some patients died before the Rx became available but none now die on it.

2a Systematic review with homogeneity of cohort studies

2b Individual cohort study (including low quality RCT; e.g., <80% follow-up)

2c "Outcomes" Research (relates the health and clinical outcome of a cohort of patients with the same diagnosis to the care that they received)

3a Systematic review with homogeneity of case-control studies

3b Individual case-control study

3c Individual controlled cross-sectional study

4 Observational studies without controls (case series, before-and-after studies, prevalence cross-sectional studies) and poor quality cohort and case control studies

5 Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" (i.e. the pathophysiological principles used to determine clinical practice).

Table 4
Classification of recommendations for clinical management:

I	Strong recommendation for use in clinical management, arising from strong evidence obtained from Class A and B studies.
II	Recommendation for clinical management that is based on Class B and/or Class C evidence.
III	Suggestion for clinical management that is based on Class D evidence and/or where evidence is inconclusive.

How can we best detect early respiratory insufficiency?

Since death in MND/ALS patients is frequently due to ventilatory failure caused by respiratory muscle weakness, it is important to manage dyspnoea and hypoventilation, including sleep-disordered breathing, from as early a stage as possible. This can help the discussion about mechanical ventilation, which can prolong survival (Lyall et al, 2001b; Sherman & Paz, 1994). Whilst respiratory symptoms are an insensitive marker for pulmonary impairment, they can alert the clinician to the possibility of respiratory muscle weakness (Lechtzin et al, 2002; Lyall, Moxham & Leigh, 2000; Miller et al, 1999; Borasio, Gelinas & Yanagisawa, 1998). Sometimes forced vital capacity and arterial blood gas measurements may remain normal despite presence of chronic hypoventilation (Borasio, Gelinas & Yanagisawa, 1998). In this instance, patients' self-reported symptoms can indicate respiratory insufficiency and help in determining the use of non-invasive ventilation (Gonzalez-Lorenzo & Diaz-Lobato, 2000; Lyall, Moxham & Leigh, 2000; Borasio, Gelinas & Yanagisawa, 1998; Braun, 1987). Table 5 outlines the main symptoms and signs. It should be noted that symptoms of respiratory insufficiency or hypercapnia can be subtle if they are not looked for specifically (Lyall, Moxham & Leigh, 2000; Hardiman, 2000; Miller et al, 1999). It is recommended that signs of respiratory

Table 5
Symptoms and Signs of Respiratory Insufficiency.

Symptoms	Signs
Breathlessness on exertion (dyspnoea)	Reduced chest expansion
Breathlessness when lying down (orthopnoea)	Rapid Respiratory Rates
Morning headaches	Accessory muscle recruitment
Extreme fatigue	Weak cough
Excessive daytime sleepiness	Weak sniff
Disturbed sleep or frequent nocturnal awakenings	Paradoxical movement of the abdomen on inspiration
Nightmares	
Anxiety	
Impaired cognition	
Decreased appetite	

insufficiency be checked regularly.
According to Miller et al (1999), there is no evidence for the best test of detection of early signs of impending respiratory failure. It is also unknown at what level of respiratory muscle weakness, hypoventilation occurs (Lyall et al, 2001b). Furthermore there is no single test of respiratory muscle strength, which can predict hypercapnia reliably, although all measurements of respiratory muscle strength have been shown to have prognostic value (Lyall et al, 2001b). Initial clinical measurements can include slow vital capacity, static inspiratory and expiratory mouth pressures, maximal sniff oesophageal pressure, maximal sniff trans-diaphragmatic pressure, sniff nasal inspiratory pressures, cough gastric pressure, testing serum bicarbonate and chloride levels and blood gases. A combination of respiratory muscle strength or pulmonary function measures is demonstrated throughout the literature and it is thus recommended that such a procedure be followed rather than reliance on one particular test.

Spirometry is useful in detecting early respiratory involvement in MND/ALS and in predicting the course of respiratory failure (Schiffman & Belsh, 1993; Poloni et al, 1983). Spirometry may consist of forced expiratory volume in one second (FEV1), a flow-volume loop and slow vital capacity (VC) measurements in a sitting/standing or lying position on a volumetric spirometer. Forced vital capacity (FVC) is the most utilised form of monitoring respiratory function in neuromuscular patients (Varrato et al, 2001) and its results have been shown to be reproducible with less than 5% variability (Andres et al, 1988). As MND/ALS develops, there is a progressive reduction in vital capacity, which is related to muscular weakness and vital capacity declines at an accelerated rate towards the end of the terminal stage (Lyall et al, 2001b; Melo et al, 1999; Escarrabill et al, 1998; Poloni et al, 1983). A decrease in VC to 50% predicted is associated with respiratory symptoms and VC is considered to be predictive of survival time (Varrato et al, 2001; Miller et al, 1999). As Stambler et al (1998) demonstrated, the lower the vital capacity, the shorter the survival time in MND/ALS. Varrato et al (2001) compared the measures of erect, seated forced vital capacity (eFVC) and supine forced vital capacity (sFVC) in a cohort study and concluded that supine FVC is significantly lower and the erect minus supine FVC difference (e-sFVC) is significantly greater in MND/ALS patients with complaints of dyspnoea and orthopnoea. Diaphragmatic weakness was also strongly associated with daytime fatigue. In spite of an e%FVC about 50%, patients with diaphragmatic weakness are at risk for nocturnal hypoventilation during non-REM and REM sleep. This indicates that sFVC and e-sFVC should be included in the routine monitoring of respiratory function in patients with MND/ALS, particularly in those with respiratory symptoms even if the e%FVC is significantly greater than 50% (Varrato et al, 2001).

However, vital capacity can be an insensitive test of respiratory muscle function in the early and later stages of the disease and patients with pseudobulbar features or bulbar onset disease cannot use the test accurately (Hadjikoutis & Wiles, 2001; Chaudri et al, 2000; Fitting et al, 1999; Miller et al, 1999). Forced vital capacity can remain normal despite substantial inspiratory muscle weakness (Lechtzin et al, 2002). Marti-Fabregas et al (1996) found in a case series study that while FVC results were useful for determining the presence and degree of respiratory system involvement, FVC deterioration showed a curvilinear slope rather than a linear correlation with survival in the later stages of the disease. These results have been disputed in studies such as Schiffman & Belsh (1996). Another spirometry measure, the maximal voluntary ventilation (MVV), has been proposed as a single measure of both inspiratory and expiratory respiratory function and like FVC, MVV correlates with survival (Fallat et al, 1979; Griggs, 1990). MVV is not routinely offered in most UK lung function laboratories. Chaudri et al (2000) argue that despite the insensitivity of vital capacity, it is a good index of respiratory function and they recommend the combination of vital capacity with sniff nasal inspiratory pressure in assessments of respiration.

Sniff nasal inspiratory pressure (SNIP) has been advocated as a better predictor of respiratory failure than vital capacity as it is more sensitive to decrements in inspiratory muscle strength (Lyall et al, 2001a; Lyall et al, 2001b; Chaudri et al, 2000; Fitting et al, 1999). Fitting et al (1999) demonstrated in a study of 16 patients that sniff nasal inspiratory pressure was the most useful single respiratory test which showed sensitivity in mild disease and feasibility in advance disease, where maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were not possible. Maximal inspiratory pressure and maximal expiratory pressure are the standard tests of inspiratory and expiratory muscle strengths (Lechtzin et al, 2002). Sniff nasal inspiratory pressure was also easy to perform and inexpensive and similar to forced vital capacity, sniff nasal inspiratory pressure was suitable for assessing the linear decline of respiratory muscle strength in MND/ALS (Fitting et al, 1999). Another case series of 59 MND/ALS patients concluded that SNIP was a simple and alternative

measure to vital capacity and was better than MIP and MEP in identifying patients with hypercapnia. This was replicated by Lyall et al (2001b) in their study of 81 MND/ALS patients, where SNIP was a better predictor of hypercapnia in patients without significant bulbar involvement. Patients with a sniff nasal inspiratory pressure of 30% of the predicted value are at risk of developing hypercapnia and it is recommended that their arterial blood gas levels be measured (Chaudri et al, 2000). However, in patients with bulbar involvement SNIP is not as sensitive in predicting hypercapnia (Lyall et al, 2001b; Chaudri et al, 2000). Another alternative to maximal mouth pressures (MIP and MEP) as shown in a cohort study is the use of a 'whistle', a test where pressure is measured at the mouth during a short, sharp and maximal expiration through a narrow aperture (Chetta et al, 20001). This is a non-invasive and uncomplicated manoeuvre of expiratory muscle strength and can be used in addition to maximal static expiratory effort (Chetta et al, 2001), although the results need to be reproduced in other studies on MND/ALS patients.

Diaphragm electromyography (EMG) has also been used to detect respiratory insufficiency (Stewart et al, 2001; Similowski et al, 2000; Chen et al, 1997). Electrophysiological studies of the respiratory system can demonstrate early and severe involvement of the diaphragm relative to the other muscles in respiratory failure (Chen et al, 1997; de Carvalho et al, 1996) and the relationship of the diaphragm to dyspnoea has promoted Similowski et al (2000) to recommend diaphragm function tests once symptoms of dyspnoea occur. In a retrospective study of 52 MND/ALS patients, the procedure was found to be safe to use on MND/ALS patients at or around time of diagnosis and could detect sub-clinical respiratory muscle dysfunction (Stewart et al, 2001). At present, EMG is used in research rather than in the clinical setting.

Recommendations:

1. To detect respiratory insufficiency, check the symptoms and signs suggestive of respiratory insufficiency - see box (III).
2. Perform respiratory function tests in any patient who develops symptoms or signs suggestive of respiratory insufficiency. Use vital capacity standing or seated (if possible supine) and sniff nasal inspiratory pressure (SNIP) to measure inspiratory function and to assess expiratory function, use peak expiratory flow rate during forced expiration and cough flow (II).
3. Use signs of respiratory insufficiency to estimate respiratory function in patients with severe bulbar disease who cannot manage to perform respiratory function tests and measure arterial blood gases (including bicarbonate) (III).

What are the recommended procedures for monitoring respiratory function?

Clinical vigilance, serial measurements of vital capacity, nocturnal hypoventilation and coughs and advance planning are recommended in the literature for managing respiratory problems in the MND/ALS patient. A multi-disciplinary approach to management is advocated including contributions from neurologists, occupational therapists, speech therapists, nurse care managers, social workers, physiotherapists, physciatrists and respiratory specialists (Benditt, 2002; Richard & Rome, 2000). This ties in with the overall recommendation of a multidisciplinary approach to the provision of care for the MND/ALS patient (Sufit, 1997; Tandan & Bradley, 1985).

Quality of life is correlated with respiratory symptoms (Bourke et al, 2001). Clinicians should therefore routinely check symptoms and signs of early respiratory insufficiency (Bradley et al, 2002; Melo et al, 1999). It is advisable that respiratory function is measured as soon as the diagnosis is made (Schilz & Marlow, 2001; Fallat et al, 1987). Routine assessments can include quality of life instruments or questionnaires designed to monitor progression of disability in the patient. For example, the ALS Functional Rating Scale (ALSFRS) was recently revised to include assessments of respiratory function (Cedarbaum et al, 1999). Dougan et al (2000) developed a dyspnoea specific questionnaire for MND/ALS patients, which could measure the physical and psychological components of dyspnoea but it needs to be further validated and tested on a wider population.

Regular monitoring of vital capacity is also recommended as it is beneficial to the evaluation of declining respiratory function, though no specific frequency is determined (Miller et al, 1999). Braun (1987) suggests measuring FEV1, FVC, MVV, peak cough flows and arterial blood gases at 6-month intervals if no respiratory symptoms occur (grade 5). Crocker Houde & Mangolds (1999) propose that a nurse practitioner measure respiratory status every 3 months. Variance in phonation time has been seen to correlate with nearly 50% of the variability of vital capacity and so successive measurements of phonation time can be used to estimate the loss of vital capacity (Hillel et al, 1989). A chest radiograph is considered important when ventilatory function deteriorates suddenly, as these patients are at risk for aspiration and infection (Leigh & Ray-Chaudhuri, 1994). In addition, Leigh & Ray-Chaudhuri (1994) propose testing cough strength and the ability to count up to 20 in one breath. Repeated use of other measurements of respiratory system such as diaphragm function tests are also endorsed throughout the literature.

Sleep disturbance or nocturnal hypoventilation is one of the earliest indications of respiratory insufficiency in MND/ALS, as alveolar hypoventilation occurs during the hours of sleep before clinical or daytime symptoms become apparent (Miller et al, 1999; Ferguson et al, 1996). Sleep-disturbance in MND/ALS patients has been associated in a cohort study with a reduction in respiratory muscle strength (Ferguson et al, 1996). In another cohort study, Arnulf et al (2000) demonstrated that there was a significant reduction in rapid eye movement (REM) sleep duration in MND/ALS patients with diaphragm dysfunction (REM-related desaturations are causes of sleep disruption). This was linked with a higher risk of respiratory disorders and a shorter median survival time than those without diaphragmatic dysfunction (Arnulf et al, 2000). Gay et al (1991a) and Velasco et al (2002) also associated survival time with symptoms of sleep disruption, nocturnal oximetry and pulmonary function in their case series studies. Varrato et al (2001) propose use of polysomnography or nocturnal oximetry in all patients with symptoms consistent with sleep disordered breathing even with FVC about 50% predicted. Kimura et al (1999) concluded from their cohort study that monitoring of the respiratory function during sleep should be initiated in the routine evaluation of MND/ALS patients at the early clinical stage. Gay et al (1991a) recommend a routine screening of MND/ALS patients with spirometry, questions about quality of sleep and outpatient overnight oximetry. Frequent follow up with questionnaires assessing sleep hygiene and an objective determination of nocturnal hypoventilation can also assist in the institution of non-invasive ventilation (Sivak et al, 2001; Gay et al, 1991a).

As MND/ALS patients develop expiratory muscle weakness and bulbar dysfunction, their cough becomes ineffective and the clearance of respiratory secretions becomes problematic. This can lead to mucus plugging, atelectasis and chest infections (Lecthtzin et al, 2002). An impaired cough is not a prognostic factor but may have a role in identifying patients who need to be monitored more closely (Chaudri et al, 2002). The use of peak cough flow and peak expiratory flow are useful in monitoring expiratory muscle weakness and bulbar involvement in respiratory insufficiency (Suarez et al, 2000). The ability to generate a peak cough flow of at least 160 litres per minute was found to be necessary for successful removal of a tracheostomy tube in neuromuscular patients (Suarez et al, 2000) and for clearing secretions (Polkey et al, 1998). Kang & Bach (2000) found a correlation between vital capacity, maximum insufflation capacity and unassisted and assisted peak cough flows. The group whose maximum insufflation capacity was greater than their forced vital capacity showed greater significant increase in the peak cough flows and the ability to expel airway mucus and avert respiratory complications. They concluded that maximal insufflations are important to increase peak cough flows in patients with neuromuscular conditions and who have vital capacities of less than 1500ml (Kang & Bach, 2000).

Recommendations:

1. Perform respiratory function testing (FVC) in all patients every 3 months (II).
2. The presence of symptoms suggestive of nocturnal hypoventilation should prompt a study of sleep. Use overnight oximetry as a screening tool (II).
3. Since abnormal blood gases and nocturnal hypoventilation are indicators for urgent evaluation for non-invasive ventilation or alternate symptom control, measure arterial blood gases and perform overnight oximetry/$TcCO_2$ monitoring in any patient with symptoms suggestive of nocturnal hypoventilation (II).

How can respiratory insufficiency be managed?

The communication with the patient and family about breathing difficulties and treatment options is an essential component of the management of respiratory insufficiency. Patients and carers should be informed about the signs and symptoms of respiratory infections and the importance of reporting any changes in respiratory function or secretions (Crocker Houde & Mangolds, 1999). It is also widely recommended through grade 4 and 5 studies that patients be advised about non-invasive ventilation, invasive ventilation and the terminal phase from the onset of management of respiration. Since use of mechanical ventilation often occurs when there is an acute respiratory insufficiency, it is important that the patient and carer are aware as early as possible about the benefits and limitations of mechanical ventilation and the possible choice of palliative care (Lyall, Moxham & Leigh, 2000; Escarrabill et al, 1998; Cazzolli & Oppenheimer, 1996). The decision-making should take into account the level of care provided both by the family and by the patient's health care system, the financial resources available as well as the patient's desires (Hardiman, 2000; Sufit, 1997). Dyspnoea often causes anxiety in the patient and such concerns also need to be addressed, along with coping strategies for handling respiratory emergencies (Schonhofer & Kohler, 1998; Borasio & Voltz, 1997; Kristjanson, Nelson & Henteleff, 1987). Ability to control discontinuation of ventilation is crucial to ALS patients' decision on whether or not to start ventilation and physicians' attitudes should be conveyed and discussed as part of the patients' information on ventilatory support (Shneerson & Simmonds, 2002; Simmonds, 2000). Specific advance directives are emphasised as being crucial to the management of respiration (Shneerson & Simmonds, 2002; Gonzalez-Lorenzo & Diaz-Lobato, 2000; Simmonds, 2000; Lyall, Moxham & Leigh, 2000; Borasio & Voltz, 1998; Sufit, 1997). These should take place before respiratory failure (Schilz & Marlow, 2001). Should patients decline use of non-invasive ventilation or cannot tolerate it, patients should be informed about the terminal phase, hospice referral and palliative care (Miller et al, 1999).

Dyspnoea can be palliated with drugs such as benzodiazepines and opioids (Benditt, 2002; Lyall, Moxham & Leigh, 2000). Borasio & Voltz (1997) suggest the administration of morphine for reducing the subjective feeling of shortness of breath and Borasio, Voltz & Miller (2001) argue that titration of the morphine dose against the clinical effect almost never leads to a life threatening depression of respiratory drive. Anxiety attacks can occur due to dyspnoea and this may be treated with short acting anxiolytics, such as 0.5 to 2.0mg lorazepam sublingually. For pulmonary infections, the use of antibiotics may be helpful (Langton Hewer, 1995). Richard & Rome (2000) advise that anxiolytic and hypnotic drugs be avoided as they may lead to acute respiratory failure (grade 5). In the terminal stages, dyspnoea can be relieved using opioids (Miller et al, 1999). Schonhofer & Kohler (1998) suggest the administration of morphine, bronchoscopic suction and insufflation of oxygen. Oxygen therapy has been used to supplement ventilatory support in the short term, especially during acute pneumonia (Shneerson & Simmonds, 2002) but a case-series study found that oxygen therapy could be disadvantageous to neuromuscular patients (Gay & Edmonds, 1995). Until more research is done, caution is recommended in the administration of oxygen to MND/ALS patients.

In relation to procedures that can help relieve symptoms of dyspnoea other than drugs or non-invasive ventilation, Schilz & Marlow (2000) advise good nutrition and rest as aids to respiration. Hardiman (2000) and Langton Hewer (1995) suggest that patients be told to sleep in a semi-upright position with support pillows and that techniques to reduce the risk of aspiration should be introduced, including suction machines, alteration in food texture and advice regarding swallowing (grade 5).

Most of the evidence in this area comes from clinical experience and opinion apart from two studies on the effects of medication on dyspnoea and respiratory muscles. Creatine supplementation was found in a case series study to have had no long-term effect on the function of respiratory muscles in MND/ALS patients (Drory & Gross, 2002) and while Schiffman & Belsh (1989) imply in their placebo-controlled small scale study that theophylline could strengthen respiratory muscles, this has not yet been validated in other studies on MND/ALS patients. There is one study (grade 4) that showed a positive effect of ventilatory muscle training on improving ventilatory capacity, pulmonary functions and inspiratory force in neuromuscular disease patients, including six with MND/ALS (Gross & Meiner, 1993). The ventilatory muscle training involved resistive breathing as a prophylactic treatment for 10 minutes, three times daily. The study is too small scale to be applicable to the wider MND/ALS population and while Schiffman & Belsh (1989) also found that mildly affected MND/ALS patients responded to a respiratory resistance exercise programme, further replications are needed.

Recommendations:

1. Initiate discussions about all treatment options such as non-invasive, invasive ventilation and terminal phase as soon as symptoms or signs of respiratory insufficiency develop. Discussions should be as early as possible to enable advance planning or directives and specifically include discussion of the patient's wishes with regard to tracheostomy ventilation and or endotracheal intubation (II).
2. Consider simple measures to ease dyspnoea such as manually assisted cough, measures to avoid aspiration, sleeping in an upright position with support pillows and use of antibiotics for infections (III).
3. Use non-invasive ventilation for alleviating breathlessness and mechanical cough assist devices for improving cough (II).
4. Prescribe medication such as benzodiazepines and opioids to keep in reserve for palliation of terminal breathlessness (II).

What are the patients' and carers' views on managing difficulties with respiratory function?

Apart from one controlled cross-sectional study (McDonald, Hillel & Wiedenfeld, 1996), studies on patients' and caregivers' preferences were surveys or exploratory pieces of qualitative research on the issues of importance to the patient and primary caregiver in regards to mechanical ventilation (grade 4). Studies were largely based on the experiences of US residents (Narayanaswami et al, 2000; Albert et al, 1999; Gelinas, O'Connor & Miller, 1998; Moss et al, 1996; Moss et al, 1993). Furthermore, the emphasis was more on the views of the patients with little distinction between the perspectives of carers and patients.

Through the studies, patients reported satisfaction with their quality of life despite the drawbacks of ventilatory support. McDonald, Hillel & Wiedenfeld (1996) compared 18 MND/ALS patients with ventilatory support to 126 non-ventilatory supported MND/ALS patients in terms of physical and psychological status. While significant differences between the two groups could not be statistically observed and the study had some methodological problems, such as selection bias and a large unmatched control group, ventilatory supported patients viewed their quality of life as being acceptable (McDonald, Hillel & Wiedenfeld, 1996). Moss et al (1993) found that only 4.2% (15) of 355 MND/ALS patients on home ventilation in northern Illinois had chosen home ventilation but that the majority of these were happy with their decision. This was also echoed in their later study (Moss et al, 1996). Gelinas, O'Connor & Miller (1998) indicated that satisfaction with quality of life might be linked to the length of time on a ventilator. In interviews with 7 ventilator dependent MND/ALS patients and 11 caregivers, those who were 2 years or more on a ventilator were more satisfied with the decision than those who had ventilatory support for less than 2 years. All expressed disappointment with the difficulty in the transition to ventilator (Gelinas, O'Connor & Miller, 1998). When compared to patients with Duchenne muscular dystrophy (DMD) matched on demographics, MND/ALS patients were less likely to be satisfied with quality of life on a ventilator (Narayanaswami et al, 2000). The authors attributed this negativity to the comparatively faster progression of physical disability in MND/ALS compared to DMD patients.

MND/ALS patients were adamant that the decision in regards to use of mechanical ventilation was solely theirs. Young, Marshall & Anderson (1994) interviewed 13 patients in order to explore the process and factors involved in decision making in regards to mechanical ventilatory support. All maintained that it was exclusively their decision and factors which influenced their decision were quality of life, severity of disability, availability of ventilation by means of a nasal mask, ability to discontinue use of mechanical ventilator and possible admission to a long-term care facility. Better communication between health professionals and patients in regards to decision making was advocated, especially the inclusion of information on the patient's expected course, the effects to family life and the major expenses involved (Moss et al, 1996; Young, Marshall & Anderson, 1994). Moss et al (1996) surveyed the decision-making process and patient preferences amongst 75 MND/ALS patients who were on long term mechanical ventilation. The majority reported that they felt well prepared to make a decision about long term mechanical ventilation. While 75% were aware that they were likely to develop respiratory failure, only 42% had made their decision in advance of a crisis. Many had advance directives involving the withdrawal of mechanical ventilation in certain circumstances (Moss et al, 1996).

Prior knowledge and favourable disposition towards mechanical ventilation appears to influence decision-making for the patient. Albert et al (1999) found an association between use of mechanical ventilation and

favourable views in a survey of 121 MND/ALS patients in a USA care centre. Those in favour of the use of tracheostomy and bi-level positive airway pressure ventilators favourably at baseline were significantly more likely to use the intervention over the follow up period. Patients who find the interventions acceptable were also more likely to be recently diagnosed, expressed greater attachment to life and showed great declines in pulmonary function over follow up.

In relation to caregivers' views, carers frequently highlighted poor access to patient management, health complaints, financial strain, restricted activities and less freedom to leave the house (Bromberg et al; 1996; Moss et al, 1993). They also found the adjustment to ventilatory support difficult and that the ventilator responsibilities were time consuming (Gelinas, O'Connor & Miller, 1998). In an exploratory study on the experiences of 38 Dutch patients with neuromuscular disease and their family members, emotional stress was reported to have increased over time amongst the carers of patients on tracheostomy (van Kestern, Velthusis & van Leyden, 2001). Family members had to be available 24 hours a day and required psychosocial support, voluntary assistance and professional home care (van Kestern, Velthusis & van Leyden, 2001). Overall, carers were generally satisfied with quality of life of patients on mechanical ventilation (Gelinas, O'Connor & Miller, 1998; Bromberg et al; 1996; Moss et al, 1993) and cited continued family life as a benefit (Moss et al, 1993).

Recommendations:

1. MND/ALS patients and their carers should be consulted and fully informed about the management of respiratory insufficiency. Their views should be taken into account when deciding the interventions (II). (In the context of public provision in the UK patients should be aware that tracheostomy ventilation may precipitate the need to move to a specialised care setting).
2. Review the patient's wishes regarding their care and if advance directive in place review regularly (II).
3. All patients who are being considered for respiratory interventions should be referred to a palliative care team, either before respiratory intervention or at the time of respiratory intervention

Can non-invasive ventilation help respiratory insufficiency in MND/ALS?

1. *Types of non-invasive interventions.*

Non-invasive and invasive mechanical ventilations are used to alleviate respiratory symptoms in MND/ALS patients and to prolong survival. Invasive ventilators are administered via a tracheostomy or endotracheal tube, whilst non-invasive ventilators are applied directly to the face or body using a nasal, face-mask or mouth-piece (Shneerson & Simmonds, 2002). Non-invasive mechanical ventilators can be either negative-pressure or positive-pressure devices. The former passively expands the chest and increases the inspiratory volume. An example is the cuirass or chest shell and the 'rocking bed'. These have the disadvantage of patients having to lie on their back throughout the night but can, theoretically be used in patients who do not tolerate positive pressure techniques (Shneerson & Simmonds, 2002; Chalmers et al, 1994). However in such patients progressive weakness of the upper airway musculature may lead to the development of obstructive sleep apnoea during negative pressure ventilation. Furthermore, two observational studies from the mid 1990s found that negative-pressure body ventilators can be effective in aiding survival in neuromuscular patients (Corrado et al, 1994; Chalmers et al, 1994). These results need further validation in MND/ALS patients.

Positive-pressure ventilators are currently the more popular form of non-invasive ventilation techniques offered in the USA and in Europe. These devices administer pressurised air to the lungs through the naso-oropharynx; various machines are available. The most important distinction is between continuous positive airway pressure (CPAP), which is not suitable for the treatment if respiratory insufficiency due to MND/ALS and non-invasive positive-pressure ventilators (NIPPV) which may be subdivided into machines which give pressure only in inspiration and those which also maintain a pressure in expiration. This latter type of NIPPV is termed bi-level positive airway pressure, Non-invasive positive pressure ventilation has become a standard procedure in ALS centres in the USA, though there are variations in its usage in Europe (Miller et al, 1999; Borasio et al, 1998). It does not require an artificial airway and as a result, it does not impair speech, swallowing or coughing during the day. Moreover, it can be used at home. Disadvantages include complications such as nasal ulcers, mask displacement, and air leaks(Shneerson & Simmonds, 2002). Continuous positive airway pressure is used for patients with sleep

apnoea but is not considered appropriate for patients with MND/ALS as it still requires inspiratory muscle contraction to generate inspiratory airflow (Borasio, Gelinas & Yanagisawa, 1998). No direct data are available to address whether the bi-level sub-type of NIPPV is preferred in ALS/MND. The choice of bi-level positive airway pressure machine is likely to be determined by local and individual issues. It is typically administered via a mask or nasal pillow and used for 6 to 8 hours during sleep.

Although randomised controlled trials are yet to be undertaken on the use of mechanical insufflator-exsufflators and cough assist devices, there are some observational studies that suggest their facilitation in sputum clearance in patients with an acute chest infection and overt respiratory failure (Shneerson & Simmonds, 2002; Lechtzin et al, 2002; Bach, 1995b). Assisted coughing techniques, such as the patient or carer providing a manual abdominal thrust as the patient coughs, may also be effective (Lyall, Moxham & Leigh, 2000). Manual assisted expiration and other suitable forms of physiotherapy may also help (Richard & Rome, 2000; Langton Hewer, 1995). Cough in-exsufflators can be used when cough expiratory flow falls to <160 $Lmin^{-1}$ (Shneerson & Simmonds, 2002). If assisted cough techniques are ineffective, tracheostomy has been used for clearances of secretions (Lechtzin et al, 2002).

Choice of ventilation will depend upon a range of factors including availability, cost, patient preference and the presence of other symptoms such as upper airway obstruction or bronchial secretions (Borasio, Gelinas & Yanagisawa, 1998). Non-invasive positive pressure ventilation is reported to be more favourable with MND/ALS patients than invasive ventilation and thus non-invasive ventilation should be considered before tracheostomy (Miller et al, 1999). However, there is some evidence that patients who start mechanical ventilation using non-invasive ventilators are more likely to refuse invasive ventilation later on (Escarrabill et al, 1998; Cazzolli & Oppenheimer, 1996).

2. *Timing of non-invasive ventilation.*

Miller et al (1999) stated that determining the timing of initiation of non-invasive mechanical ventilation is crucial as there is the risk of sudden death or ventilator dependence without proper advance planning. Yet, there are still no prospective or randomised controlled trials that determine the indications for initiating non-invasive ventilation. In the absence of such trials, information on the timing of intervention has to be drawn from observational studies, which are hindered by their ability to make associations and correlations rather than establishing cause and effect.

There is some disagreement in the literature to the timing of intervention. Miller et al (1999) recommend intervention once respiratory symptoms appear or when FVC is less than 50%. In practice, Bourke et al (2002) found in their survey of UK neurologists that respiratory symptoms are the main indication for use of non-invasive ventilation. For example, a weakened diaphragm in the initial signs of progressive ventilatory failure can prompt early use of non-invasive ventilatory support. Such a practice has been linked in observational studies to the possibility of significant improvement in respiration, after the diaphragm has been rested for a period with ventilatory assistance (de Carvalho et al, 1996). This needs more cohort and experimental studies to establish this effect of the intervention. Hadjikoutis & Wiles (2001) assessed the use of domiciliary venous serum chloride and bicarbonate measurements in evaluating respiratory function in MND/ALS patients in a case series and concluded that they provide useful information about respiratory status and prognosis in MND/ALS patients. Since NIPPV and other non-invasive ventilation techniques are primarily used to alleviate respiratory symptoms, both objective measures and subjective reports are important.

In relation to FVC, Melo et al (1999) disagree with the level set by Miller et al (1999) and argue that intervention should be when FVC is less than 70% predicted or when a serum chloride level is below normal limits (<98 mEq/1). Cazzolli & Oppenheimer (1996) also use FVC of less than 50% and state that respiratory impairment can also be detected by a maximum inspiratory force of –30cm H_2O or less or by a maximum expiratory force of 30 cm H_2O or less. Other studies have found a poor correlation or association between vital capacity and initiation of non-invasive positive-pressure ventilators (NIPPVs). Jackson et al (2001) randomised patients to receive non-invasive positive pressure ventilation upon nocturnal oximetry studies (oxygen desaturations being less than 90%) or a FVC < 50% predicted. They found that maximal inspiratory pressure and nocturnal oximetry were more sensitive physiological markers of early respiratory insufficiency. Sivak et al (2001) observed 27 MND/ALS patients who tolerated NIPPV for more than 4 hours per 24-hour period for more than 2 weeks and concluded that there was a lack of correlation between

vital capacity at institution of NIPPV and duration of effectiveness. This led them to conclude that more sensitive indicators for the onset of alveolar hypoventilation are needed, especially since the principal benefit is relief of alveolar hypoventilation. Most studies argue that nocturnal hypoventilation should be taken as the initial sign for non-invasive ventilation, such as NIPPV, particularly since it is an effective treatment for nocturnal hypoventilation (Shneerson & Simmonds, 2002; Sivak et al, 2001; Jackson et al, 2001). This suggests that non-invasive ventilation should be initiated earlier than the recommendation of Miller et al (1999). Polysomnography or nocturnal oximetry & capnometry can be used to identify patients who may be helped by non-invasive ventilation (Sivak et al, 2001; Jackson et al, 2001; Gay et al, 1991a).

It should be noted that in MND/ALS patients, loss of bulbar muscle tone and difficulty in clearing secretions can affect the patient's tolerance of non-invasive ventilation (Miller et al, 1999; Aboussouan et al, 1997; Cazzolli & Oppenheimer, 1996; Howard, Wiles & Loh, 1989). Respiratory assessment should therefore include an evaluation of bulbar dysfunction (Hadijikoutis & Wiles, 2001). NIPPV is also unlikely to benefit patients without symptoms (Shneerson & Simonds, 2002). Invasive ventilation may be considered for patients with moderate or severe bulbar symptoms who are unable to tolerate NIPPV (but it must be stressed that availability and support may be a problem in UK at present).

3. *Effects of non-invasive ventilation on quality of life and survival rates.*

NIPPV, can reverse respiratory failure and improve symptoms in neuromuscular and chest wall diseases and improve general quality of life (Sivak et al, 2001; Lyall et al, 2001a; Aboussouan & Lewis, 1999; Aboussouan et al, 1997; Pinto et al, 1995; Braun et al, 1987). Physical activity, haemodynamics, normalisation of blood gases and slight improvement in vital capacity and other physiological measures such as maximal mouth pressure have also been reported (Shneerson & Simonds, 2002; Sivak et al, 2001). Non-invasive ventilation is also a more cost-effective alternative to tracheostomy, as it does not require nurses to help with regular home care (Ginsberg & Lowe, 2002).

Case series studies such as Gay et al (1991b) report that nocturnal non-invasive ventilation improves alveolar ventilation and arterial oxygenation and as a result, the patients who tolerated non-invasive ventilation considered their quality of life to have improved. Bilevel pressure support devices can also improve overnight arterial blood gas control, cause upper airway stabilisation and can reduce atelectasis in the patient. (Shneerson & Simmonds, 2002). A cohort study by Aboussouan et al (2001) showed that while non-invasive ventilation may improve quality of life compared to those who were intolerant of it, it had no impact on the rated of decline of lung function. Forced vital capacity and forced expiratory volume in the first second (FEV1) continued to decline (2.3% and 2.09% predicted points per month respectively), although for some patients it did show improvement indices of respiratory muscle strength and increased FVC or FEV_1 on initiation of non-invasive ventilation. More studies are needed on the impact of the unloading effect of non-invasive ventilation on respiratory muscle function.

Quality of life as measured by SF-36 has been shown to increase significantly only for mental health component in patients with MND/ALS on NIPPV, though overall quality of life was shown to have remained stable under home mechanical ventilation despite progression of disease (Hein, Schucher & Magnussen, 1999). Furthermore, quality of life for MND/ALS patients with home mechanical ventilation was higher when compared to hospital mechanical ventilation (Saito, 1999; Bach, 1993). In a cohort study conducted by Lyall et al (2001a), quality of life of 16 patients ventilated with NIPPV was assessed using SF-36 questionnaire and compared to a control group who had normal diaphragm function and no respiratory symptoms. Quality of life of MND/ALS patients with sleep disordered breathing improved significantly with NIPPV with higher scores than seen at the baseline. This was maintained despite increased generalised disability and progressive respiratory muscle weakness. Another cohort study (Newsom Davies et al, 2001) attempted to evaluate the effect of NIPPV on cognitive function in MND/ALS patients. Nocturnal hypoventilation and sleep disturbance can cause cognitive dysfunction, such as affected memory, and these deficits were significantly improved by NIPPV over a six-week period (Newsom Davies et al, 2001). Non-invasive ventilation has generated fears that it protracts death rather than extend good quality of life and that it inevitably leads to invasive ventilation (Shneerson & Simmonds, 2002). This fear should be addressed when conveying information on management for respiratory insufficiency.

Observational studies have suggested that continuous use of non-invasive ventilation can prolong life survival in

MND/ALS patients who can tolerate it (Bach, 2002; Buhr-Schinner, Laier-Groeneveld & Criee, 1999; Schlamp et al, 1998; Aboussouan et al, 1997; Cazzolli & Oppenheimer, 1996; Pinto et al, 1995; Bach, 1995a). A cohort study (grade 2b) conducted by Winterholler et al (2001) observed the long- term effects and complications of non-invasive ventilation in 31 neuromuscular patients, including 20 MND/ALS patients. Mean survival to death, tracheostomy or withdrawal of treatment was 248 days in MND/ALS without bulbar symptoms (SE +/- 35.7) and 82 days for those with bulbar symptoms (SE +/- 27.4) compared to 2052 days in the slowly progressive neuromuscular disease group. They concluded that non-invasive ventilation is beneficial to MND/ALS patients without bulbar symptoms for up to a year (Winterholler et al, 2001). Another case series found that selected symptomatic patients who were allocated NIPPV had a median survival of 10 months (Polkey et al, 1999), while Cazzolli & Oppenheimer (1996) observed a prolongation of survival for 6 to 64 months if NIPPV was used 20 to 24 hours a day. Aboussouan et al (1997) found that 46% of hypercapnic and/or orthopnoeic patients were able to tolerate NIPPV. Patients who tolerated NIPPV tended to live longer than those who did not. This was replicated in a later cohort study (Aboussouan et al, 2001). In a case series of 101 patients by Bach (2002), continuous use of NIPPV, with mechanically assisted coughing using oximetry, was seen to prolong survival by delaying the need for tracheostomy for more than a year. Bach (1995a) attempted to determine in a case series of 27 MND/ALS patients, the pulmonary function variables that best predicted the prolonging of survival in MND/ALS patients with using non-invasive respiratory aids. The ability to generate assisted peak cough expiratory flows (PCEF) in excess of 3L/sec and the ability to hold an insufflation deeper than vital capacity were associated with the capacity to prolong survival when using non-invasive ventilatory support (Bach, 1995a).

In relation to bi-level positive airway pressure, an observational study (grade 4) by Kleopa et al (1999) attempted to assess the utility of bi-level positive airway pressure in prolonging survival in MND/ALS patients. 122 patients were offered Bi-level positive airway pressure when their FVC had dropped to below 50% of the predicted value. Some refused the treatment, others tried it but did not tolerate it and a third group tolerated bi-level positive airway pressure and used it for more than 4 hours a day. From the comparisons, Kleopa et al (1999) concluded that all patients with a FVC of less than 50% predicted, with symptoms of dyspnoea or have had a rapid drop in FVC should be offered bi-level positive airway pressure as bi-level positive airway pressure could significantly prolong survival in the late stages of MND/ALS and slow the decline of FVC in MND/ALS. Pinto et al (1995) also found a survival advantage in non-invasive ventilated patients when compared to those who did not receive bi-level positive airway pressure. A later small-scale cohort study by Pinto et al (1999b) suggests that a combination of bi-level positive airway pressure and exercise (if muscle strength is above 3 on the MRC scale) can help prolong survival. More studies are warranted to address issues of tolerance, quality of life and optimal time of bi-level positive airway pressure initiation. Overall, experimental research – particularly randomised controlled trials - is needed on the effects of non-invasive ventilation on quality of life and survival for patients with MND/ALS.

Some ventilators intended for home use are not intended to be run 24 hours/day. In patients with advanced disease who are ventilator dependent it is good practice to ensure both that the patient has access to an alternative power source (eg battery pack) as well as a second machine in case of mechanical failure.

Recommendations

1. Offer non-invasive ventilation to patients as there is evidence showing that it improves quality of life and survival. (II).
2. The choice of machine used to give non-invasive ventilation can be reasonably determined by individual clinical details as well as local availability and expertise, since both have been shown to be effective in MND/ALS patients (II).
3. Offer non-invasive ventilation to patients with daytime symptoms of nocturnal hypoventilation and mild bulbar symptoms (II).
4. Use non-invasive cough-assist devices, if available, in patients with a weak cough who develop a lower respiratory tract infection (III) or if also using NIPPV use physiotherapy assisted by NIPPV.
5. In patients with advanced disease who are ventilator dependent it is good practice to ensure both that the patient has access to an alternative power source (e.g. battery pack) as well as a second machine in case of mechanical failure

Can invasive ventilation help respiratory insufficiency in MND/ALS?

Impaired ventilatory function usually occurs late in the course of ALS but occasionally can happen shortly after the onset of symptoms. It is at this point that patients, carers and clinicians should consider invasive ventilatory support (Miller et al, 1999). Borasio et al (2001) found that in European centres, tracheostomy is routinely discussed when the patient first shows symptoms of chronic nocturnal hypoventilation or has first dyspnoeic symptoms or when vital capacity falls below 50%. Cedarbaum & Stambler (2001) retrospectively evaluated the experience of 387 placebo patients (from a multi-centre randomised controlled trial of recombinant brain-derived neurotrophic factor in MND/ALS) on when they began using mechanical ventilatory aids. Continuous mechanical ventilation was instigated in patients with a mean FVC of 30% and intermittent mechanical ventilation in patients with a mean FVC of 50% (Cedarbaum & Stambler, 2001). Invasive mechanical ventilation has also been reported to be commonly used for acute episodes of respiratory failure, such as infections of the upper or lower respiratory tract (Corrado et al, 1995).

In relation to long-term invasive mechanical ventilation, the American Association for Respiratory Care has developed a clinical practice guideline for its provision in the home (AARC, 1995). To be eligible for invasive long-term ventilatory support, patients need to have demonstrated an inability to be completely weaned from invasive ventilatory support or have a progression of disease aetiology that requires increasing ventilatory support (AARC, 1995). For MND/ALS patients, Sivak, Cordasco and Gipson (1983) suggest consideration of long term home ventilation using tracheostomy when a patient cannot be weaned from mechanical ventilation either by intermittent mandatory ventilation or by a graduated T-piece method. Failure of the weaning process is defined as the inability to maintain adequate ventilation (Pa CO_2 <50mmHG, Pa O_2 > 65mmHG, with FiO_2 < 30%) for at least 10 hours (AARC, 1995).

Quality of life for the patient can be improved through the use of mechanical ventilation despite decline in physical function (Shneerson & Simonds, 2002; Lyall et al, 2001a; Winterholler et al, 2001; Camu, 2001; Miller et al, 1999; Kondo & Shinkai, 1996; Bach, 1993; Howard, Wiles & Loh, 1989). Since quality of life is related to respiratory muscle function (Bourke et al, 2001), it can be surmised that relief of respiratory symptoms would improve quality of life. Both non-invasive and invasive ventilation can alleviate the symptoms of hypoventilation and dyspnoea (Newsom-Davies et al, 2001; Miller et al, 1999).

The goal of long-term invasive mechanical ventilation is to prolong patient survival and to improve or to sustain the physical and psychological functions of the ventilator-assisted patient (AARC, 1995). A cohort study (grade 2b) was conducted by Albert et al (1999) on the use of palliative care amongst 121 MND/ALS patients, including effects of tracheostomy on survival. Use of palliative care at last follow up interval was compared with outcome at baseline for two groups – newly diagnosed and long term patients – over a 12 month period. Survival benefit of tracheostomy was evident in the lower mortality of the long-term group compared to the recently diagnosed (32% vs. 53.8%, $p < 0.05$). Unlike other palliative endpoints measure, tracheostomy was rare within the first 2 years of diagnosis. Cazzolli & Oppenheimer (1996) have also demonstrated in a case series that use of tracheostomy can prolong survival for approximately 10 years. However, invasive ventilation can be expensive, necessitates ongoing tracheal suctioning, requires 24 hour nursing care and places personal stress on patients and on the caregivers (Miller et al, 1999; Saito, 1999; Borasio, Gelinas & Yanagisawa, 1998; Bach, 1993; Tandan & Bradley, 1985; Sivak, Cordasco & Gipson, 1983). Kaub-Wittemer et al (2003) demonstrated in their case series that the burden of care was high for caregivers, with 30% of the fifty-two carers rating their own quality of life as being much lower than their patients. Ventilator dependent patients do require a lot of support and this can make use of invasive ventilation in the home very difficult, though it is less costly than institutional care (Ginsberg & Lowe, 2002; Escarrabill et al, 1998; Tandan & Bradley, 1985; Sivak, Cordasco & Gipson, 1983). Use of a multidisciplinary team approach including psychological support is recommended for supporting ventilation in the home (Lyall, Moxham & Leigh, 2000; Kondo & Shinkai, 1996; Sivak, Cordasco & Gipson, 1983; Sivak et al, 1981).

Recommendations:

1. Consider invasive ventilation electively when non-invasive ventilation is not tolerated due to bulbar symptoms and when non-invasive ventilation is no longer effective due to progression of disease (II).
2. Invasive ventilation improves quality of life and survival for patients and should be considered for all appropriate patients, on the basis of a fully informed decision by the patient and carer (II).
3. Discuss fully the negative implications of use of invasive ventilation with patients and carers and use advance directives to avoid unplanned emergency intubation (II).

What is the optimal method of withdrawing both invasive and non-invasive ventilation from patients with MND/ALS?

Invasive Ventilation.

The degree of respiratory support for MND/ALS patients increases with the progression of the disease. As a result, independence from the ventilator is rarely achieved (Bradley et al, 2002). According to legal and ethical precedents, a mentally competent and informed patient has the right to refuse or discontinue any treatment, including life support and mechanical ventilation (Hardiman, 2000; Miller et al, 1999). Polkey et al (1999) argue that withdrawal of the ventilator should be ideally dictated by patient preference. Since the MND/ALS patient can become completely dependent upon ventilator support, they may be unable to communicate their wishes. It is thus advisable to have advance directives concerning which circumstances will trigger withdrawal of the ventilator (Gonzalez-Lorenzo & Diaz-Lobato, 2000; Miller et al, 1999; Polkey et al, 1999; Moss et al, 1996). The discussion for withdrawal should be as early as possible. Although not specifically on MND/ALS patients, Way et al (2002) conducted a review on advance directives and concluded that it is essential to be aware that there can be differences in interpretation of the procedure so discussions need to be conducted carefully with the patients and their families.

Borasio & Voltz (1998) argue that the question of withdrawal can only be meaningfully addressed in the context of palliative care. The recommended course of action to a patient's request for life-support withdrawal is withdrawal with either prophylactic or subsequent sedation, with drugs such as opioids and benzodiazepines which can be used as a palliative measures to prevent terminal dyspnoea (Polkey et al, 1999). It is crucial that the sedation is not too light as it might not relieve dyspnoea nor can it be too high a dose, which could kill a patent before hypoxia does. Intention should be to relieve suffering not to hasten death, even though death may be a consequence of the action (Miller et al, 1999). The primary aim in the initiation of ventilatory withdrawal is to maintain patient comfort (Bradley et al, 2002; Miller et al, 1999). Supplemental oxygen (if used) and positive expiratory pressure should firstly be discontinued, followed by the conversion to a T-piece and spontaneous breathing (Miller et al, 1999). The use of neuromuscular blocking agents is strictly contraindicated, as patients may not be able to express pain or distress (Gelinas & Miller, 2000). Gradual withdrawal from ventilator allows gradual development of hypercapnia and provide terminal coma but medication is still required (Polkey et al, 1999).

Non-Invasive Ventilation.

Stopping non-invasive ventilation has identical legal implications though it may be emotionally less stressful if the patients condition has not advanced so far as to preclude enough time for appropriate palliative measures to be installed (Borasio & Voltz, 1998).

Recommendations:

1. Advance directives are very helpful and should be reviewed periodically (II).
2. Since a mentally competent and informed patient has the right to refuse or discontinue any treatment including life support and mechanical ventilation, those responsible for care must not prolong ventilation against the patients will (III).
3. If withdrawal is requested, appropriate treatment should be continued to ensure symptoms such as anxiety, distress and discomfort are managed effectively (III)

Conclusion:

The purpose of this systematic review was to develop evidence based guidelines for the management of respiration in MND/ALS patients. Until more evidence is produced these guidelines are based on current evidence of best practice, which largely comprises of observational research and clinical opinion. Much of this may be case series, uncontrolled prospective studies and small-scale cohort studies but their presence is adequate for the production of guidelines until higher quality studies are produced. There is a need for further evidence, in particular randomised and non-randomised controlled trials on the effects of non-invasive ventilation and additional larger scale cohort studies on the more ethically potent issues of timing of interventions and initial assessment of respiratory symptoms and management of respiration.

Development Group

Mary-Ann Ampong, Clinical Nurse Specialist
Catherine Heffernan, Guidelines Researcher
Crispin Jenkinson, Professor of Health Services Research
Will Kinnear, Respiratory Physician
Nigel Leigh, Professor of Neurology
Heidi Macleod, MND Association
David Oliver, Palliative Care Consultant

Peer Reviewed by:
Michael Polkey Consultant Respiratory Physician
Nigel Sykes, Medical Director, St Christopher's Hospice

Respiratory References

1995, "AARC clinical practice guideline: long-term invasive mechanical ventilation in the home", *Respiratory Care*, vol. 40, no. 12, pp. 1313-1320.

Aboussouan, L. S., Khan, S. U., Meeker, D. P., Stelmach, K., & Mitsumoto, H. 1997, "Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis", *Ann Intern Med*, vol. 127, no. 6, pp. 450-453.

Aboussouan, L. S. & Lewis, R. A. 1999, "Sleep, respiration and ALS", *J Neurol Sci*, vol. 164, no. 1, pp. 1-2.

Aboussouan, L. S., Khan, S. U., Banerjee, M., Arroliga, A. C., & Mitsumoto, H. 2001, "Objective measures of the efficacy of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis", *Muscle Nerve*, vol. 24, no. 3, pp. 403-409.

Albert, S. M., Murphy, P. L., Del Bene, M. L., & Rowland, L. P. 1999, "Prospective study of palliative care in ALS: choice, timing, outcomes", *J Neurol Sci*, vol. 169, no. 1-2, pp. 108-113.

Albert, S. M., Murphy, P. L., Del Bene, M. L., & Rowland, L. P. 1999, "A prospective study of preferences and actual treatment choices in ALS", *Neurology*, vol. 53, no. 2, pp. 278-283.

Andres, P., Finison, L., Conlon, T., & Munsat, T. Use of composite scores (megascores) to measure deficit in amyotrophic lateral sclerosis. Neurology 38, 405-408. 2003. Ref Type: Journal (Full)

Arnulf, I., Similowski, T., Salachas, F., Garma, L., Mehiri, S., Attali, V., Behin-Bellhesen, V., Meininger, V., & Derenne, J. P. 2000, "Sleep disorders and diaphragmatic function in patients with amyotrophic lateral sclerosis", *Am J Respir Crit Care Med*, vol. 161, no. 3 Pt 1, pp. 849-856.

Bach, J. R. 1993, "Amyotrophic lateral sclerosis. Communication status and survival with ventilatory support", *Am J Phys Med Rehabil.*, vol. 72, no. 6, pp. 343-349.

Bach, J. R. 1995, "Amyotrophic lateral sclerosis: predictors for prolongation of life by noninvasive respiratory aids", *Arch-Phys-Med-Rehabil.*, vol. 76, pp. 828-832.

Bach, J. R. 1995, "Respiratory muscle aids for the prevention of pulmonary morbidity and mortality", *Seminars-in-Neurology.*, vol. 15, no. 1, pp. 72-83.

Bach, J. R. 2002, "Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory aids", *Chest*, vol. 122, no. 1, pp. 92-98.

Barthlen, G. M. 1997, "Nocturnal respiratory failure as an indication of noninvasive ventilation in the patient with neuromuscular disease", *Respiration*, vol. 64 Suppl 1, pp. 35-38.

Benditt, J. O. 2002, "Respiratory complications of amyotrophic lateral sclerosis", *Seminars-in-Respiratory-and-Critical-Care-Medicine.*, vol. 23, no. 3, pp. 239-247.

Borasio, G. D. & Voltz, R. 1997, "Palliative care in amyotrophic lateral sclerosis", *J Neurol*, vol. 244 Suppl 4, p. S11-S17.

Borasio, G. D., Gelinas, D. F., & Yanagisawa, N. 1998, "Mechanical ventilation in amyotrophic lateral sclerosis: a cross-cultural perspective", *J Neurol*, vol. 245 Suppl 2, pp. S7-12.

Borasio, G. D. & Voltz, R. 1998, "Discontinuation of mechanical ventilation in patients with amyotrophic lateral sclerosis", *J Neurol*, vol. 245, no. 11, pp. 717-722.

Borasio, G. D., Shaw, P. J., Hardiman, O., Ludolph, A. C., Sales-Luis, M. L., & Silani, V. 2001, "Standards of palliative care for patients with amyotrophic lateral sclerosis: results of a European survey", *Amyotroph.Lateral Scler.Other Motor Neuron Disord.*, vol. 2, no. 3, pp. 159-164.

Borasio, G. D., Voltz, R., & Miller, R. G. 2001, "Palliative care in amyotrophic lateral sclerosis", *Neurologic Clinics*, vol. 19, no. 4, pp. 829-847.

Bourke, S. C., Shaw, P. J., & Gibson, G. J. 2001, "Respiratory function vs sleep-disordered breathing as predictors of QOL in ALS", *Neurology*, vol. 57, no. 11, pp. 2040-2044.

Bourke, S. C., Williams, T. L., Bullock, R. E., Gibson, G. J., & Shaw, P. J. 2002, "Non-invasive ventilation in motor neuron disease: current UK practice", *Amyotroph.Lateral Scler.Other Motor Neuron Disord.*, vol. 3, no. 3, pp. 145-149.

Bradley, M. D., Orrell, R. W., Clarke, J., Davidson, A. C., Williams, A. J., Kullmann, D. M., Hirsch, N., & Howard, R. S. 2002, "Outcome of ventilatory support for acute respiratory failure in motor neurone disease", *J Neurol Neurosurg Psychiatry*, vol. 72, no. 6, pp. 752-756.

Braun, S. R. 1987, "Respiratory system in amyotrophic lateral sclerosis", *Neurol Clin*, vol. 5, no. 1, pp. 9-31.

Braun, S. R., Sufit, R. L., Giovannoni, R., O'Connor, M., & Peters, H. 1987, "Intermittent negative pressure ventilation in the treatment of respiratory failure in progressive neuromuscular disease", *Neurology*, vol. 37, no. 12, pp. 1874-1875.

Bromberg, M. B., Forshew, D. A., Iaderosa, S., & McDonald, E. R. 1996, "Ventilator dependency in ALS: management, disease progression, and issues of coping", *J-Neurol-Rehabil.*, vol. 10, pp. 195-216.

Buhr-Schinner, H., Laier-Groeneveld, G., & Criee, C. P. 1999, "Die amyotrophe Lateralsklerose unter intermittierender Selbstbeatmungstherapie. [Amyotrophic lateral sclerosis and nasal mechanical ventilation]", *Med Klin*, vol. 94, no. 1 Spec No, pp. 102-104.

Camu, W. 2001, "Troubles respiratoires du sommeil dans la sclerose laterale amyotrophique. [Respiratory disorders during sleep in amyotrophic lateral sclerosis]", *Rev Neurol (Paris)*, vol. 157, no. 11 Pt 2, p. S152-S155.

Cazzolli, P. A. & Oppenheimer, E. A. 1996, "Home mechanical ventilation for amyotrophic lateral sclerosis: nasal compared to tracheostomy-intermittent positive pressure ventilation", *J Neurol Sci*, vol. 139 Suppl, pp. 123-128.

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., & Nakanishi, A. 1999, "The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III)", *J Neurol Sci*, vol. 169, no. 1-2, pp. 13-21.

Cedarbaum, J. M. & Stambler, N. 2001, "Disease status and use of ventilatory support by ALS patients. BDNF Study Group", *Amyotroph.Lateral Scler.Other Motor Neuron Disord.*, vol. 2, no. 1, pp. 19-22.

Chalmers, R. M., Howard, R. S., Wiles, C. M., & Spencer, G. T. 1994, "Use of the rocking bed in the treatment of neurogenic respiratory insufficiency", *QJM*, vol. 87, no. 7, pp. 423-429.

Chaudri, M. B., Liu, C., Watson, L., Jefferson, D., & Kinnear, W. J. 2000, "Sniff nasal inspiratory pressure as a marker of respiratory function in motor neuron disease", *European-Respiratory-Journal.*, vol. March, 15, pp. 539-542.

Chaudri, M. B., Liu, C., Hubbard, R., Jefferson, D., & Kinnear, W. J. 2002, "Relationship between supramaximal flow during cough and mortality in motor neurone disease", *Eur.Respir J*, vol. 19, no. 3, pp. 434-438.

Chen, R., Grand', m. F., Brown, J. D., & Bolton, C. F. 1997, "Motor neuron disease presenting as acute respiratory failure: Electrophysiological studies", *Muscle-and-Nerve.*, vol. 20, no. 4, pp. 517-519.

Chetta, A., Harris, M. L., Lyall, R. A., Rafferty, G. F., Polkey, M. I., Olivieri, D., & Moxham, J. 2001, "Whistle mouth pressure as test of expiratory muscle strength", *Eur.Respir J*, vol. 17, no. 4, pp. 688-695.

Chio, A. & Silani, V. 2001, "Amyotrophic lateral sclerosis care in Italy: a nationwide study in neurological centers", *J Neurol Sci*, vol. 191, no. 1-2, pp. 145-150.

Corrado, A., Gorini, M., & De Paola, E. 1995, "Alternative techniques for managing acute neuromuscular respiratory failure", *Seminars-in-Neurology.*, vol. 15, no. 1, pp. 84-89.

Crocker Houde, S. & Mangolds, V. Amytrophic Lateral Sclerosis: A team approach to primary care. Clinical Excellence.for Nurse Practitioners 3[6], 337-345. 1999. Ref Type: Journal (Full)

Culebras, A. 1996, "Sleep and neuromuscular disorders", *Neurol Clin*, vol. 14, no. 4, pp. 791-805.

De Carvalho, M., Matias, T., Coelho, F., Evangelista, T., Pinto, A., & Luis, M. L. 1996, "Motor neuron disease presenting with respiratory failure", *J Neurol Sci*, vol. 139 Suppl, pp. 117-122.

Dougan, C. F., Connell, C. O., Thornton, E., & Young, C. A. 2000, "Development of a patient-specific dyspnoea questionnaire in motor neurone disease (MND): the MND dyspnoea rating scale (MDRS)", *J Neurol Sci*, vol. 180, no. 1-2, pp. 86-93.

Drory, V. E. & Gross, D. 2002, "No effect of creatine on respiratory distress in amyotrophic lateral sclerosis", *Amyotroph.Lateral Scler.Other Motor Neuron Disord.*, vol. 3, no. 1, pp. 43-46.

Escarrabill, J., Estopa, R., Farrero, E., Monasterio, C., & Manresa, F. 1998, "Long-term mechanical ventilation in amyotrophic lateral sclerosis", *Respir Med*, vol. 92, no. 3, pp. 438-441.

Fallat, R. J., Jewitt, B., Bass, M., Kamm, B., & Norris, F. H. Spirometry in amyotrophic lateral sclerosis. Arch Neurol 36, 74-80. 1979. Ref Type: Journal (Full)

Fallat, R. J., Norris, F. H., Holden, D., Kandal, K., & Roggero, P. C. 1987, "Respiratory monitoring and treatment: objective treatments using non-invasive measurements", *Adv Exp Med Biol*., vol. 209, pp. 191-200.

Ferguson, K. A., Strong, M. J., Ahmad, D., & George, C. F. 1996, "Sleep-disordered breathing in amyotrophic lateral sclerosis", *Chest*, vol. 110, no. 3, pp. 664-669.

Fitting, J. W., Paillex, R., Hirt, L., Aebischer, P., & Schluep, M. 1999, "Sniff nasal pressure: a sensitive respiratory test to assess progression of amyotrophic lateral sclerosis", *Ann Neurol*, vol. 46, no. 6, pp. 887-893.

Galinsky, M. D., Malaguti, R., Andres, P., & Munsat, T. 1996, "Amyotrophic lateral sclerosis: a comprehensive review", *Physician Assistant*, vol. 20, no. 8, p. 65.

Gay, P. C., Westbrook, P. R., Daube, J. R., Litchy, W. J., Windebank, A. J., & Iverson, R. 1991, "Effects of alterations in pulmonary function and sleep variables on survival in patients with amyotrophic lateral sclerosis", *Mayo Clin Proc*., vol. 66, no. 7, pp. 686-694.

Gay, P. C., Westbrook, P. R., Daube, J. R., Litchy, W., Windebank, A., & Iverson, R. Nocturnal nasal ventilation for treatment of patients with hypercapnic respiratory failure. Mayo-Clinic-Proceedings. 66, 695-703. 1991. Ref Type: Journal (Full)

Gay, P. C. & Edmonds, L. C. 1995, "Severe hypercapnia after low-flow oxygen therapy in patients with neuromuscular disease and diaphragmatic dysfunction", *Mayo Clin Proc*., vol. 70, no. 4, pp. 327-330.

Gelinas, D. & Miller, R. C. 2000, "A treatable disease: a guide to the management of amyotrophic lateral sclerosis," in *Amyotrophic Lateral Sclerosis*., R. H. Brown, V. Meninger, & M. Swash, eds., Martin Duntz, London, pp. 405-422.

Gelinas, D. F., O'Connor, P., & Miller, R. G. 1998, "Quality of life for ventilator-dependent ALS patients and their caregivers", *J Neurol Sci*, vol. 160 Suppl 1, p. S134-S136.

Ginsberg, G. & Lowe, S. 2002, "Cost effectiveness of treatments for amyotrophic lateral sclerosis: a review of the literature", *Pharmacoeconomics*., vol. 20, no. 6, pp. 367-387.

Gomez-Fernandez, L. & Calzada-Sierra, D. J. 2001, "Importancia del tratamiento rehabilitador multifactorial en la esclerosis lateral amiotrofica. [The importance of multifactorial rehabilitation treatment in amyotrophic lateral sclerosis]", *Rev Neurol*, vol. 32, no. 5, pp. 423-426.

Griggs, R. C. The use of pulmonary function testing as a quantitative measurement for therapeutic trials. Muscle-and-Nerve. 13[suppl], S30-S34. 1990. Ref Type: Journal (Full)

Gross, D. & Meiner, Z. 1993, "The effect of ventilatory muscle training on respiratory function and capacity in ambulatory and bed-ridden patients with neuromuscular disease", *Monaldi-Archives-for-Chest-Disease*, vol. 48, no. 4, pp. 322-326.

Hadjikoutis, S. & Wiles, C. M. 2001, "Respiratory complications related to bulbar dysfunction in motor neuron disease", *Acta-Neurologica-Scandinavica*, vol. 103, no. april, pp. 207-213.

Hadjikoutis, S. & Wiles, C. M. 2001, "Venous serum chloride and bicarbonate measurements in the evaluation of respiratory function in motor neuron disease", *QJM*, vol. 94, no. Sept, pp. 491-495.

Hardiman, O. 2000, "Symptomatic treatment of respiratory and nutritional failure in amyotrophic lateral sclerosis", *J Neurol* , vol. 247, no. 4, pp. 245-251.

Hein, H., Schucher, B., & Magnussen, H. 1999, "Intermittierende Selbstbeatmung bei neuromuskularen Erkrankungen: Verlauf und Lebensqualitat. [Intermittent assisted ventilation in neuromuscular diseases: course and quality of life]", *Pneumologie*, vol. 53 Suppl 2, p. S89-S90.

Hetta, J. & Jansson, I. 1997, "Sleep in patients with amyotrophic lateral sclerosis", *J Neurol*, vol. 244, no. 4 Suppl 1, p. S7-S9.

Hillel, A. D., Yorkston, K., & Miller, R. M. 1989, "Using phonation time to estimate vital capacity in amyotrophic lateral sclerosis", *ARCH PHYS MED REHABIL*, vol. 70, no. 8, pp. 618-620.

Howard, R. S., Wiles, C. M., & Loh, L. 1989, "Respiratory complications and their management in motor neuron disease", *Brain* , vol. 112, no. Pt 5, pp. 1155-1170.

Jackson, C. E., Rosenfeld, J., Moore, D. H., Bryan, W. W., Barohn, R. J., Wrench, M., Myers, D., Heberlin, L., King, R., Smith, J., Gelinas, D., & Miller, R. G. 2001, "A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients", *J Neurol Sci*, vol. 191, no. 1-2, pp. 75-78.

Kamimoto, K., Murakami, N., Muroga, T., Matsubara, M., & Yamamoto, M. 1989, "[A comparative study between amyotrophic lateral sclerosis patients with and without mechanical ventilation]", *Rinsho Shinkeigaku*, vol. 29, no. 8, pp. 989-993.

Kang, S. & Bach, J. R. Vital capacity and cough flows in neuromuscular disease. Am-J-Phys-Med-Rehabil. 79, 222-227. 2000. Ref Type: Journal (Full)

Kaub-Wittemer, D., von Steinbuchel, N., Wasner, M., Laier-Groeneveld, G., & Borasio, D. Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers. Journal of Pain and Symptom Management 26[4], 890-896. 2003. Ref Type: Journal (Full)

Kimura, K., Tachibana, N., Kimura, J., & Shibasaki, H. 1999, "Sleep-disordered breathing at an early stage of amyotrophic lateral sclerosis", *J Neurol Sci*, vol. 164, no. 1, pp. 37-43.

Kleopa, K. A., Sherman, M., Neal, B., Romano, G. J., & Heiman-Patterson, T. 1999, "Bipap improves survival and rate of pulmonary function decline in patients with ALS", *J Neurol Sci*, vol. 164, no. 1, pp. 82-88.

Kondo, K. & Shinkai, T. 1996, "Home ventilation for amyotrophic lateral sclerosis patients," in *Amyotrophic Lateral Sclerosis: Progress and Perspectives in Basic Research and Clinical Application*, I. Nakano & A. Hirano, eds., Elsevier, Amsterdam, pp. 388-392.

Kristijanson, L. J., Nelson, F., & Henteleff, P. D. Palliative care for individuals with amyotrophic lateral sclerosis. Journal of Palliative Care 2[2], 28-34. 1987. Canada: Clinical Research Inst of Montreal/Ctr for Bioethics. Ref Type: Journal (Full)

Langton Hewer, R. 1995, "The Management of Motor Neuron Disease," in *Motor Neurone Disease: Biology and Management*, P. N. Leigh & M. Swash, eds., Springer-Verlas, London, pp. 375-406.

Lechtzin, N., Weiner, C. M., & Clawson, L. 2001, "A fatal complication of noninvasive ventilation", *N Engl J Med*, vol. 344, no. 7, p. 533.

Lechtzin, N., Rothstein, J., Clawson, L., Diette, G. B., & Wiener, C. M. 2002, "Amyotrophic lateral sclerosis: evaluation and treatment of respiratory impairment", *Amyotroph.Lateral Scler.Other Motor Neuron Disord.*, vol. 3, no. 1, pp. 5-13.

Leigh, N. & Ray-Chaudhuri, K. Motor Neuron Disease. Journal of Neurology, Neurosurgery and Psychiatry 57, 886-896. 1994. Ref Type: Journal (Full)

Lyall, R. A., Moxham, J., & Leigh, N. 2000, "The control of symptoms. 4.1 Dyspnoea.," in *Palliative Care in Amyotrophic Lateral Sclerosis (Motor Neurone Disease)*, 1st edn, D. Oliver, G. D. Borasio, & D. Walsh, eds., Oxford University Press, Oxford, pp. 43-62.

Lyall, R. A., Donaldson, N., Fleming, T., Wood, C., Newsom-Davis, I., Polkey, M. I., Leigh, P. N., & Moxham, J. 2001, "A prospective study of quality of life in ALS patients treated with noninvasive ventilation", *Neurology*, vol. 57, no. 1, pp. 153-156.

Lyall, R. A., Donaldson, N., Polkey, M. I., Leigh, P. N., & Moxham, J. 2001, "Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis", *Brain*, vol. 124, no. Pt 10, pp. 2000-2013.

Marti, F. J., Sanchis, J., Casan, P., Miralda, R., Garcia, P. E., & Illa, I. 1996, "Forced vital capacity deterioration in amyotrophic lateral sclerosis has an inflexion point", *EUR J NEUROL*, vol. 3, no. 1, pp. 40-43.

McDonald, E. R., Hillel, A., & Wiedenfeld, S. A. 1996, "Evaluation of the psychological status of ventilatory-supported patients with ALS/MND", *Palliat Med*, vol. 10, no. 1, pp. 35-41.

Melo, J., Homma, A., Iturriaga, E., Frierson, L., Amato, A., Anzueto, A., & Jackson, C. 1999, "Pulmonary evaluation and prevalence of non-invasive ventilation in patients with amyotrophic lateral sclerosis: a multicenter survey and proposal of a pulmonary protocol", *J Neurol Sci*, vol. 169, no. 1-2, pp. 114-117.

Miller, R. G., Rosenberg, J. A., Gelinas, D. F., Mitsumoto, H., Newman, D., Sufit, R. L., Borasio, G. D., Bradley, W. G., Bromberg, M. B., Brooks, B. R., Kasarskis, E. J., Munsat, T. L., & Oppenheimer, E. A. 1999, "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", *Neurorehabilitation.and Neural Repair*, vol. 13, no. 2, pp. 93-107.

Moss, A. H., Casey, P., Stocking, C. B., Roos, R. P., Brooks, B. R., & Siegler, M. 1993, "Home ventilation for amyotrophic lateral sclerosis patients: outcomes, costs, and patient, family, and physician attitudes", *Neurology*, vol. 43, no. 2, pp. 438-443.

Moss, A. H., Oppenheimer, E. A., Casey, P., Cazzolli, P. A., Roos, R. P., Stocking, C. B., & Siegler, M. 1996, "Patients with amyotrophic lateral sclerosis receiving long-term mechanical ventilation. Advance care planning and outcomes", *Chest*, vol. 110, no. 1, pp. 249-255.

Narayanaswami, P., Bertorini, T. E., Pourmand, R., & Horner, L. H. 2000, "Long-term tracheostomy ventilation in neuromuscular diseases: patient acceptance and quality of life", *Neurorehabilitation.and Neural Repair*, vol. 14, no. 2, pp. 135-139.

Newsom-Davis, I. C., Lyall, R. A., Leigh, P. N., Moxham, J., & Goldstein, L. H. 2001, "The effect of non-invasive positive pressure ventilation (NIPPV) on cognitive function in amyotrophic lateral sclerosis (ALS): a prospective study", *J Neurol Neurosurg Psychiatry*, vol. 71, no. 4, pp. 482-487.

Peruzzi, A. C. & Potts, A. F. 1996, "Physical therapy intervention for persons with amyotrophic lateral sclerosis", *Physiother-Canada.*, vol. 48, pp. 119-126.

Pinto, A. C., Evangelista, T., Carvalho, M., Alves, M. A., & Sales-Luis, M. L. 1995, "Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial", *J Neurol Sci*, vol. 129 Suppl, pp. 19-26.

Pinto, A. C., Evangelista, T., De Carvalho, M., Paiva, T., & Lurdes-Sales-Luis, M. 1999, "Respiratory disorders in ALS: sleep and exercise studies", *J Neurol Sci*, vol. 169, no. 1-2, pp. 61-68.

Pinto, A. C., Alves, M., Nogueira, A., Evangelista, T., Carvalho, J., Coelho, A., De Carvalho, M., & Sales-Luis, M. L. 1999, "Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise?", *J Neurol Sci*, vol. 169, no. 1-2, pp. 69-75.

Polkey, M., I, Lyall, R. A., Davidson, A. C., Leigh, P. N., & Moxham, J. Ethical and clincial issues in the use of home non-invasive mechanical ventilation for the palliation of breathlessness in motor neurone disease. Thorax 54, 367-371. 1999. Ref Type: Journal (Full)

Polkey, M. I., Lyall, R. A., Green, M., Nigel-Leigh, P., & Moxham, J. 1998, "Expiratory muscle function in amyotrophic lateral sclerosis", *Am J Respir Crit Care Med*, vol. 158, no. 3, pp. 734-741.

Poloni, M., Mento, S. A., Mascherpa, C., & Ceroni, M. 1983, "Value of spirometric investigations in amyotrophic lateral sclerosis", *Ital.J Neurol Sci*, vol. 4, no. 1, pp. 39-46.

Richard, I. & Rome, J. 2000, "Terminal Care in amyotrophic lateral sclerosis," in *Amyotrophic Lateral Sclerosis*, R. H. Brown, V. Meninger, & M. Swash, eds., Martin Dunitz, London, pp. 441-452.

Saito, T. 1999, "[Mechanical ventilation for amyotrophic lateral sclerosis—Making a comparison between hospital and home care]", *Rinsho Shinkeigaku*, vol. 39, no. 1, pp. 70-71.

Schiffman, P. L. & Belsh, J. M. 1989, "Effect of inspiratory resistance and theophylline on respiratory muscle strength in patients with amyotrophic lateral sclerosis", *Am Rev Respir Dis.*, vol. 139, no. 6, pp. 1418-1423.

Schiffman, P. L. & Belsh, J. M. 1993, "Pulmonary function at diagnosis of amyotrophic lateral sclerosis. Rate of deterioration", *Chest*, vol. 103, no. 2, pp. 508-513.

Schilz, R. & Marlow, S. 2001, "Pulmonary Management," in *Amyotrohic Lateral Sclerosis.*, H. Mitsumoto & T. Munsat, eds., Demos, New York, pp. 163-200.

Schlamp, V., Karg, O., Abel, A., Schlotter, B., Wasner, M., & Borasio, G. D. 1998, "Nichtinvasive intermittierende Selbstbeatmung (ISB) als Palliativmassnahme bei amyotropher Lateralsklerose. [Noninvasive intermittent self-ventilation as a palliative measure in amyotrophic lateral sclerosis]", *Nervenarzt*, vol. 69, no. 12, pp. 1074-1082.

Schoenhofer, B. & Koehler, D. 1998, "Options and limitations in the treatment of respiratory failure in amyotrophic lateral sclerosis", *Nervenarzt-.April,* vol. 69, no. April, pp. 312-319.

Schonhofer, B. & Kohler, D. 1998, "Therapeutische Strategien der ventilatorischen Insuffizienz bei amyotropher Lateralsklerose (ALS). Moglichkeiten und Grenzen. [Therapeutic strategies in respiratory insufficiency in amyotrophic lateral sclerosis. Possibilities and limits]", *Nervenarzt*, vol. 69, no. 4, pp. 312-319.

Sherman, M. S. & Paz, H. L. 1994, "Review of respiratory care of the patient with amyotrophic lateral sclerosis", *Respiration*, vol. 61, no. 2, pp. 61-67.

Shimizu, T., Hayashi, H., & Tanabe, H. 1991, "[Energy metabolism of ALS patients under mechanical ventilation and tube feeding]", *Rinsho Shinkeigaku*, vol. 31, no. 3, pp. 255-259.

Shimizu, T., Hayashi, H., Kato, S., Hayashi, M., Tanabe, H., & Oda, M. 1994, "Circulatory collapse and sudden death in respirator-dependent amyotrophic lateral sclerosis", *J Neurol Sci*, vol. 124, no. 1, pp. 45-55.

Shneerson, J. M. & Simonds, A. K. 2002, "Noninvasive ventilation for chest wall and neuromuscular disorders", *Eur.Respir J*, vol. 20, no. 2, pp. 480-487.

Silverstein, M. D., Stocking, C. B., Antel, J. P., Beckwith, J., Roos, R. P., & Siegler, M. 1991, "Amyotrophic lateral sclerosis and life-sustaining therapy: patients' desires for information, participation in decision making, and life-sustaining therapy", *Mayo Clin Proc.*, vol. 66, no. 9, pp. 906-913.

Similowski, T., Attali, V., Bensimon, G., Salachas, F., Mehiri, S., Arnulf, I., Lacomblez, L., Zelter, M., Meininger, V., & Derenne, J. P. 2000, "Diaphragmatic dysfunction and dyspnoea in amyotrophic lateral sclerosis", *Eur.Respir J*, vol. 15, no. 2, pp. 332-337.

Simonds, A. K. 2000, "Nasal ventilation in progressive neuromuscular disease: experience in adults and adolescents", *Monaldi Arch Chest Dis.*, vol. 55, no. 3, pp. 237-241.

Sivak, E. D., Gipson, W. T., & Hanson, M. R. 1982, "Long-term management of respiratory failure in amyotrophic lateral sclerosis", *Ann Neurol*, vol. 12, no. 1, pp. 18-23.

Sivak, E. D., Cordasco, E. M., & Gipson, W. T. Pulmonary Mechanical Ventilation at Home: A Reasonable and Less Expensive Alternative. Respiratory Care 28[1], 42-49. 1983. Ref Type: Journal (Full)

Sivak, E. D., Shefner, J. M., Mitsumoto, H., & Taft, J. M. 2001, "The use of non-invasive positive pressure ventilation (NIPPV) in ALS patients. A need for improved determination of intervention timing", *Amyotroph.Lateral Scler.Other Motor Neuron Disord.*, vol. 2, no. 3, pp. 139-145.

Stambler, N., Charatan, N., & Cedarbaum, J. M. Prognostic indicators of survival in ALS. Neurology 50, 66-72. 1998. Ref Type: Journal (Full)

Stewart, H., Eisen, A., Road, J., Mezei, M., & Weber, M. 2001, "Electromyography of respiratory muscles in amyotrophic lateral sclerosis", *J Neurol Sci*, vol. 191, no. 1-2, pp. 67-73.

Suarez, A. A., Pessolano, F. A., Monteiro, S. G., Ferreyra, G., Capria, M. E., Mesa, L., Dubrovsky, A., & De Vito, E. L. 2002, "Peak flow and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in patients with neuromuscular disease", *Am J Phys Med Rehabil.*, vol. 81, no. 7, pp. 506-511.

Sufit, R. 1997, "Symptomatic treatment of ALS", *Neurology-.*, vol. 48, p. S15-S22.

Tandan, R. & Bradley, W. G. Amyotrophic Lateral Sclerosis: Part 1. Clinical Features, Pathology, and Ethical Issues in Management. Annals of Neurology 18[3], 271-280. 1985. Ref Type: Journal (Full)

van Kesteren, R. G., Velthuis, B., & van Leyden, L. W. 2001, "Psychosocial problems arising from home ventilation", *American Journal of Physical Medicine and Rehabilitation*, vol. 80, no. 6, pp. 439-446.

Varrato, J., Siderowf, A., Damiano, P., Gregory, S., Feinberg, D., & McCluskey, L. 2001, "Postural change of forced vital capacity predicts some respiratory symptoms in ALS", *Neurology*, vol. 57, no. 2, pp. 357-359.

Velasco, R., Salachas, F., Munerati, E., Le Forestier, N., Pradat, P. F., Lacomblez, L., Orvoen-Frija, E., & Meininger, V. 2002, "Oxymetrie nocturne chez les patients atteints de sclerose laterale amyotrophique: analyse de son role predictif sur la survie. [Nocturnal oxymetry in patients with amyotrophic lateral sclerosis: role in predicting survival]", *Rev Neurol (Paris)*, vol. 158, no. 5 Pt 1, pp. 575-578.

Way, J., Back, A. L., & Curtis, J. R. Withdrawing life support and resolution of conflict with families. BMJ 325, 1342-1345. 2002. Ref Type: Journal (Full)

Winterholler, M. G., Erbguth, F. J., Hecht, M. J., Heuss, D., & Neundorfer, B. 2001, "Uberleben mit Heimbeatmung. Eine offene, prospektive Untersuchung zur Heimbeatmung bei neuromuskularen Erkrankungen unter besonderer Berucksichtigung der Situation von ALS-Patienten. [Survival with artificial respiration at home. An open, prospective study on home ventilation for neuromuscular diseases, in particular, the situation of ALS patients]", *Nervenarzt*, vol. 72, no. 4, pp. 293-301.

Young, J. M., Marshall, C. L., & Anderson, E. J. 1994, "Amyotrophic lateral sclerosis patients' perspectives on use of mechanical ventilation", *Health Soc Work*, vol. 19, no. 4, pp. 253-260.