Respiratory management of patients with amyotrophic lateral sclerosis
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Introduction
The care of patients with amyotrophic lateral sclerosis (ALS) is a very challenging but truly rewarding role for respiratory specialists. ALS is an incurable neurodegenerative disease affecting both upper and lower motor neurons, resulting in progressive skeletal muscle weakness. At onset, it generally affects predominantly either limb or bulbar muscles. Rarely, its first presentation can be respiratory failure secondary to early respiratory muscle involvement.

The median survival after onset of symptoms is 3 years. Respiratory failure, usually associated with pneumonia, is the most common cause of death. Progressive inspiratory and expiratory respiratory muscle weakness results in reduction of ventilation and cough effectiveness. Bulbar muscle involvement can also cause dysphagia and aspiration.

The only licensed drug, Riluzole, improves survival by 2-3 months. In absence of significant disease-modifying therapy, the main emphasis of care is on management of symptoms and complications of the disease. In this regard, respiratory management is of primary importance, especially since non-invasive ventilation (NIV) appears to improve both quality of life and survival. The goal of this article is to review the state of the art in respiratory management of ALS patients and to provide practical information, consistent with the recent Canadian Thoracic Society Home Mechanical Ventilation guideline, to clinicians caring for this population.

Respiratory assessment and follow-up
Patients should have a respiratory assessment at diagnosis and every two to six months depending on disease progression. This evaluation should include review of relevant symptoms and performance of pulmonary function testing (PFT) (Table 1).

Pulmonary function measurements have important prognostic value and some are better predictors of survival than ALS functional rating scales. Evolution of the disease varies significantly between individuals. Regular PFT performance demonstrates the rate of decline and identifies when significant pulmonary impairment is reached since this may be difficult to assess on clinical basis. Timing of some interventions, such as cough-assisting techniques, NIV and gastrostomy feeding tube, relies on knowledge of PFT values. Also, efficiency of airway clearance aids can be evaluated objectively by measuring peak cough flow (PCF).

Airway clearance
Invariably, the ability to adequately cough and clear secretions from airways becomes impaired with disease progression. The cough reflex involves a near-maximal inspiration followed by closure of the glottis, contraction of expiratory muscles to further increase intrathoracic pressure and finally sudden glottic opening resulting in forceful expiration. In ALS, reduced cough efficacy is related to inspiratory and expiratory muscle weakness as well as glottic impairment. Retained secretions in the airways reduce ventilation and predispose to pneumonia and respiratory failure.

Cough effectiveness can be easily measured using a peak flow meter with the patient forcibly coughing into a mouth piece or a face mask. A minimal PCF of 160 L/min has been demonstrated necessary to prevent reintubation of patients with neuromuscular disease, irrespective of their breathing capacity. However, a PCF < 270 L/min identifies individuals with neuromuscular diseases, including ALS, at risk of respiratory complications and who benefit from preventive airway clearance techniques. This is the accepted target value for introducing airway clearance management both by the Canadian and American Thoracic Societies.

When PCF is < 270 L/min and in the absence of risk for barotrauma, lung volume recruitment (LVR, a.k.a. “breath stacking”) should be introduced with measurement of assisted PCF and maximum insufflation capacity (MIC). This is usually done with a hand-held resuscitation bag via a mouthpiece or a face mask. By closing the glottis between each inspiratory volume, the patient will stack multiple breaths, reaching maximal lung volume closer to normal predicted. This volume is referred to as the MIC and is proportional to respiratory system compliance and bulbar function. LVR improves PCF and dyspnea in neuromuscular disease patients and, in the context of an airway clearance protocol, has reduced the number of hospitalizations and hospital days per year in an observational study. LVR significantly slows pulmonary function decline in Duchenne muscular dystrophy, presumably by maintaining chest wall range of motion and lung compliance.

With sufficient strength in upper extremities, patients are able to perform LVR with a hand-held resuscitation bag. When needed it can be administered by a caregiver. It is generally recommended 3 to 4 times daily, but there are no data informing the optimal frequency of sessions and number of full lung inflations during each of them.

LVR can also be done with glossopharyngeal breathing (GPB), using pharynx and tongue muscles to force boluses of air into the lungs. GPB can be taught but some patients instinctively develop this ability. Patients using noninvasive mouthpiece or invasive ventilation can use ventilator breaths to do LVR.

In all cases, manually assisted cough (MAC) can be added to LVR to further improve cough effectiveness (Figure 1). While the patient is seated or semi-recumbent, with a full lung inflation, a rapid one or two-hand abdominal thrust is applied by a caregiver below the xiphoid process just prior to glottic opening.
If, despite using LVR and MAC, the patient’s assisted PCF remains < 270 L/min or the technique cannot be performed by the patient, a trial of mechanical in-exsufflation (MI-E) is indicated. Through a face mask, a positive pressure is applied to the airway and is rapidly shifted to a negative pressure, simulating the effect of a cough. It can also be used through an artificial airway. The CoughAssist™ (Philips Respironics) is the only device available in Canada. Several case reports and observational studies have shown its utility in improving PCF, managing respiratory infection, reversing atelectasis and avoiding hospitalization. It may however be of little assistance with significant bulbar impairment and insufficient upper airway stability to maintain patency during the exsufflation phase. Its cost is approximately $5000 versus $75 for LVR with a resuscitation bag.

There are insufficient data to recommend the use of other devices such as high frequency chest wall oscillation or intrapulmonary percussive ventilation for airway clearance.

**Immunization**

Pneumococcal and annual seasonal influenza vaccination should be provided to ALS patients in accordance to the Canadian Immunization Guide.

**Dysphagia and nutrition**

Progressive bulbar impairment leads to dysphagia which often results in inadequate caloric and fluid intake and secondary worsening of weakness and fatigue. It also increases the risk of aspiration, choking and recurrent chest infection.

Initial management of dysphagia includes evaluation by a speech therapist and modification of food and fluid consistency as well as postural changes. Simultaneous care by a dietician is important to ensure adequate nutritional intake.

Percutaneous endoscopic gastrostomy (PEG) may be ultimately needed in order to provide a safe alternative route for delivering nutrition and may prolong survival, but the degree of evidence is low. Optimal timing of PEG placement is not defined, but the risk of the procedure is higher when the FVC is < 50% of predicted, which is generally considered as a relative contraindication. PEG insertion should be discussed with the patient and family members in presence of symptomatic dysphagia, weight loss or preventively, in face of declining pulmonary function.

**Sialorrhea**

Sialorrhea is a frequent symptom in ALS and is caused by oropharyngeal muscle weakness and reduced ability to swallow. It can be extremely bothersome to the patient and socially embarrassing. It can also prevent successful NIV.

Although few data are available in ALS, pharmacologic therapy is the first approach, based on information from other neurologic conditions associated with sialorrhea. Different anticholinergic medications can be used (Table 2). Suction
machines are also frequently employed for symptom control, although there is no evidence supporting their value in ALS.

When refractory to medical therapy, salivary gland injection with botulinum toxin is an option that appears to be safe and useful for treating sialorrhea in ALS patients\(^{24-25}\). Another possibility is low dose radiation therapy to the salivary glands\(^{24}\).

Patients can also complain of thick tenacious mucus, which is difficult to clear. In that case, trial of either propanalol or metoprolol may relieve symptoms\(^{26}\). Nebulized saline or N-acetylcysteine may also be useful but no controlled studies are available.

**Noninvasive ventilation**

Noninvasive ventilation (NIV) has been shown in one randomized controlled trial to improve survival (205 days (p=0.006)) and quality of life in ALS patients without severe bulbar dysfunction. In patients with poor bulbar function, NIV improved different aspects of quality of life but did not confer a survival benefit\(^4\). Four prospective and three retrospective studies also reported improved survival in ALS patients using NIV, but of modest magnitude. All studies looking at health-related quality of life showed improvement of some domains that persisted despite disease progression. Other benefits reported by different studies included improved gas exchange, reduced rate of decline in VC and enhanced cognition\(^5\).

Indications for NIV varied among the different studies which demonstrated benefit. However, some criteria are well accepted given their ability to predict hypoventilation and/or their prognostic value. These are: orthopnea, daytime hypercapnia, symptomatic sleep disordered breathing, FVC < 50% of predicted and SNP or MIP < 40 cm H\(_2\)O\(^5\) (Table 3).

NIV should be offered to ALS patients in the presence of any of these criteria. There is no evidence for suggesting where the NIV should be initiated and how to select ventilator settings. However, based on literature and CTS guidelines, ventilator parameters should be adjusted for optimal patient comfort and improvement of symptoms\(^5\). All studies that reported details of NIV used the S/T mode in which a backup rate (BUR) can be provided. There are three rationale supporting this mode over S mode: sleep disordered breathing in ALS consists mainly of REM-related non-obstructive hypopneas and central apneas\(^{27}\), patients with respiratory muscle weakness may fail to reliably trigger breaths from the bilevel device, and the BUR ensures respiratory muscle rest\(^{28}\). Arterial blood gas, nocturnal oximetry and/or polysomnography are not required but can be useful in some specific cases. Due to limited mobility and care requirements, an in-laboratory sleep study is difficult to perform for most ALS patients.

At The Ottawa Hospital CANVent Unit the first trial of NIV is made in clinic with a respiratory therapist. Bilevel ventilation in S/T with sustained inspiratory time (Ti) or PC mode, is used with the BUR set one or two breaths less than the patient’s spontaneous respiratory rate and no less than 12 breaths per minute. EPAP is generally set at 4 or 5 cmH\(_2\)O unless obstructive sleep apnea is known or suspected. IPAP is set to
achieve an estimated tidal volume of 8 to 10 ml/kg of ideal body weight and Ti is adjusted for an I:E ratio as close as possible to 1:1, considering patient comfort. Triggering, cycling and rise time are set as per patient comfort and physiology. NIV is introduced for night-time ventilation support since hypoventilation initially manifests during sleep, particularly REM stage. Those having difficulty tolerating NIV, particularly with bulbar weakness, are encouraged to begin with progressive daytime use to improve tolerance. Parameter adjustments are made on the basis of comfort, symptoms (mainly orthopnea and symptoms of sleep disordered breathing), downloaded data from the bilevel device, end-tidal CO$_2$ evolution and overnight oximetry. Nasal or oronasal interfaces can be used for NIV. Choice will rely on comfort, fitting and ease of application. A chin strap can be added to nasal masks if mouth leaks are an issue. An oronasal mask will be necessary in most patients, accepting the potential inability to remove the mask.

With disease progression, patients will require increasing daytime support and eventually continuous, 24-hour ventilation. The ability to maintain a significant MIC-VC difference and an assisted PCF > 160 L/min predicts successful use of 24-hour NIV, independently of VC or extent of need for ventilatory support. Moreover, patients with sufficiently preserved bulbar function can benefit from daytime, volume-targeted mouthpiece ventilation (MPV). By making a seal around the mouthpiece and creating a negative pressure using cheek muscles, as many breaths can be triggered as needed in order to relieve dyspnea, maintain ventilation and perform LVR. Day MPV allows for more flexibility for feeding, speech and mobility than conventional NIV. The ventilator and mouthpiece are mounted on the patient’s wheelchair (Figure 3).

**Invasive ventilation**

Those fully informed patients with bulbar impairment who cannot use 24-hour NIV and wish to survive despite severe disability will require elective tracheostomy. Tracheostomy ventilation is associated with high burden of care and many will require a chronic care facility, unless family resources are sufficient to handle such care. Tracheostomy too often results from acute respiratory failure and intubation in the absence of an advanced directive. It is critical to discuss this option with the patient and family members and to make a personal directive in order to respect the patient’s wishes. A formal education session on ventilation to the patient and caregiver is helpful in this regard.

**Diaphragm pacing**

Few data have been published on use of diaphragm pacing (DP) in ALS patients. A recent review of literature demonstrates that it appears to be reasonably safe in carefully selected patients, but it is difficult to assess its actual effectiveness in ALS. It should be noted that the majority of ALS patients using DP must simultaneously use bilevel ventilation. This device is not approved in Canada for this population and more trials are needed to confirm its utility.

**End of life**
End of life is difficult to predict but is heralded by progressive bulbar impairment, difficulty controlling oropharyngeal secretions and clearing the airway with intolerance or ineffectiveness of NIV. Involvement of palliative care in the interdisciplinary team is important. This shared care allows progressive adjustment of treatment goals with eventual provision of anxiolytics and narcotics as well as withdrawal of mechanical ventilation when appropriate.

Table 1. Respiratory assessment at each visit

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pulmonary function testing</th>
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<tbody>
<tr>
<td>Dyspnea</td>
<td>Sitting FVC</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>One or more of: Supine VC</td>
</tr>
<tr>
<td>Poor sleep</td>
<td>SNP</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>MIP</td>
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<tr>
<td>Morning headache</td>
<td>PCF spontaneously and/or assisted</td>
</tr>
<tr>
<td>Poor concentration and/or memory</td>
<td>ABG or EtCO$_2$ when hypercapnia suspected</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Nocturnal oximetry ± tCO$_2$ when symptomatic</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td></td>
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<tr>
<td>Recurrent chest infection</td>
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Table 2. Anticholinergic medications for sialorrhea treatment

<table>
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<tr>
<th>Medication</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Atropine</td>
<td>0.4 mg s/c every four to six hours</td>
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<tr>
<td></td>
<td>1% ophthalmic drops, 1-4 drops sublingual two to four times daily</td>
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<tr>
<td>Amitriptyline</td>
<td>10 to 50 mg per os once daily at bed time</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>0.2 mg s/c three times daily</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>1.5 mg transdermal patch, 1 or 2 patches applied behind ear, change</td>
</tr>
<tr>
<td></td>
<td>every 3 days</td>
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Table 3. Indications for noninvasive ventilation in ALS

- Orthopnea
- Daytime hypercapnia
- Symptomatic sleep disordered breathing
- FVC < 50% predicted
- SNP < 40 cmH$_2$O or MIP < 40 cmH$_2$O

FVC: Forced vital capacity, SNP: sniff nasal pressure, MIP: maximal inspiratory pressure
Figure 1. Lung volume recruitment (LVR) with breath stacking and effect of manually assisted cough. Adapted from ACI Respiratory Network, Domiciliary Non-Invasive Ventilation in Adult Patients (www.aci.health.nsw.gov.au)

Figure 2. Flow volume loops with and without lung volume recruitment (LVR). Red: spontaneous vital capacity. Blue: maximum insufflation capacity (MIC) with LVR.
Figure 3. ALS mouthpiece ventilation


