

# **Airway Clearance Needs in Amyotrophic Lateral Sclerosis: An Overview**

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Amyotrophic lateral sclerosis (ALS) is an insidiously progressive, fatal neurodegenerative disease that affects both the upper and lower motor neuron system. The disease was first fully described in the late nineteenth century by the French neurologist Jean-Marie Charcot and, in recognition of his contribution, is known in Europe as Charcot's disease.<sup>1</sup> In the late 1930's, ALS became popularly known in the United States as Lou Gehrig's disease, after the illness tragically ended the career of that New York Yankee baseball hero.<sup>2</sup> Other prominent individuals afflicted with ALS include astrophysicist Stephen Hawking,<sup>3</sup> composer Dimitri Shostokovich,<sup>4</sup> jazz great Charlie Mingus<sup>5</sup> and one of Franklin D. Roosevelt's vice presidents, Henry Wallace.<sup>6</sup>

ALS is a rare disease, with prevalence in the U.S. estimated between 15,000 and 30,000 cases.<sup>7</sup> Approximately 5,000 Americans are diagnosed with ALS annually; the male/female gender ratio is 2:1. Age of onset is usually between 40-70; however, ALS may afflict individuals of any age. Death occurs most frequently within 2-5 years of onset; 20% of patients survive more than 5 years, 10% more than 10 years, and a minority may live 20 or more years.<sup>8</sup> Overwhelmingly, ALS patients die as a result of pulmonary infection associated with progressive respiratory muscle weakness and eventual respiratory failure.<sup>9</sup>

Presently, ALS is an incurable disease for which there is no known cause and few effective treatments.<sup>10</sup> Between diagnosis and death, patients experience progressive muscle weakness, increasing functional disability including, frequently, loss of the ability to speak, inability to breath without mechanical assistance, and, eventually, complete motor paralysis.<sup>11</sup> The physical, emotional, social, and economic burdens of ALS are enormous.<sup>12</sup> Although responsibility for daily care falls most frequently to uncompensated family members, current average annual care costs are estimated at \$200,000 per patient.<sup>13</sup> These burdens, however, may be mitigated by rational treatment and management decisions. Emphasis should focus upon aggressive supportive treatment to preserve functional independence as long as possible. Anticipation and prevention of pulmonary complications through physician, family, and patient education can promote general health, delay the onset of pulmonary dysfunction, reduce premature mortality, costly morbidities, and unnecessary patient and caregiver quality of life deficits. In ALS, maintenance of respiratory health is the key to optimal disease management.<sup>14</sup>

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## Etiology and Pathogenesis

Although the cause of ALS remains elusive and theories of its etiology are frequently revised, four major hypotheses of ALS pathogenesis form the basis of clinical trials now in progress: excitotoxic stimulation due to accumulation of glutamate; autoimmunity; deficiency of nerve growth factor; and neuronal injury resulting from altered functioning of superoxide dismutase.<sup>15</sup> The latter hypothesis seems to apply in a recently described familial form of ALS with autosomal dominant inheritance; specific genetic markers are demonstrable in approximately 5% of cases.<sup>16</sup> Current thinking suggests that processes leading to ALS are complex and possibly interdependent, and that individuals may possess factors that increase their susceptibility for developing the disease.<sup>17</sup>

Because the etiology of ALS is unknown, specific diagnostic tests are unavailable. Diagnosis is further complicated because primary care physicians typically see patients in early stages of the disease with ill-defined symptoms including muscle cramping, twitching, vague weakness and unexplained fatigue.<sup>18</sup> However, reliable diagnosis may be made on the basis of distinct neuropathological findings, including loss and degeneration of the large anterior horn cells of the spinal cord and lower cranial motor nuclei of the brainstem. Striated muscles exhibit denervation atrophy. Diagnosis is definitive in patients demonstrating upper and lower motor neuron signs in bulbar regions and at least two spinal regions *or* in three spinal regions.<sup>19</sup> Characteristic immunohistochemical and electron micrographically demonstrable changes occur also in the upper and lower motor neurons.<sup>20</sup>

## Treatment

### Drugs

Specific treatments beneficial to ALS patients are disappointingly scarce. Although ALS is currently the focus of intensive research efforts,<sup>21</sup> riluzole, an agent that reduces the presynaptic release of glutamate, is the only known drug capable of slowing disease progression; a modest average three-month survival benefit has been demonstrated.<sup>22,23,24</sup> Based on this “success,” therapeutic trials of a variety of analogous neurotropic factors are in progress.

### Symptomatic and Supportive Care

Although ALS is incurable, it must not be regarded as untreatable. In recent years, physicians have recognized the benefits of a variety of symptomatic and supportive interventions to modify disease impact. Physical rehabilitation including the introduction of assistive devices, home healthcare equipment, nutritional, communication, and psychological support are important components of an ALS care plan. Because of the long-term implications, it is critically important for patients and their families to make informed decisions concerning non-invasive and invasive respiratory assistive devices.

However, to influence outcomes, treatment must focus upon aggressive respiratory care.<sup>25</sup> This care should include strategies to monitor pulmonary functions and infection status, to control aspiration, and to implement a regimen for effective pulmonary hygiene including airway clearance treatment.<sup>26,27</sup>

### Mechanical Ventilation

As ALS advances, failure of the respiratory system is inevitable. Although mechanical ventilation with either positive or negative pressure offers life-extending possibilities, the decision to institute such treatment is both difficult and highly individualized and involves complex ethical, financial, and legal issues. Patients, their caregivers, and their physicians must carefully consider the balance between supporting quality of life and prolonging suffering. Significant numbers of ALS patients do choose home care-based mechanical ventilation, and many report that their quality of life remains acceptable.<sup>28</sup> The use of mechanical ventilation in ALS is a multifaceted, complex topic, and will not be discussed in this context except in terms of its impact on mucus secretion and airway clearance.

## Patterns of Disease Progression

In ALS, the rate of progression of symptoms is extremely variable and generally unpredictable. Because the disease affects both upper and lower motor neurons, physical findings and symptomatology are classified respectively as bulbar features and spinal features.

### Bulbar Features

The bulbar aspects of ALS are most devastating because they involve both the ability to speak and to swallow, thus depriving patients of the fundamental pleasures of communicating and eating. Bulbar involvement varies, but as the disease progresses, swallowing, chewing, coughing, and breathing are increasingly difficult. Patients may exhibit drooping of the palate, a depressed gag reflex, dysphagia, pooling of saliva in the pharynx, a weak cough, and poor control of the tongue. The management of salivary dysphagia secondary to drooling and labial incompetence becomes progressively challenging as patients lose all ability to swallow and are ventilator-dependent. Frequently, even suction devices become inadequate. In bulbar ALS, airway patency is compromised by the aspiration of food or upper airway secretions. Sudden mucus plugging or food aspiration causes acute, sometimes prolonged hypoxia, sharply increasing risk for aspiration and aspiration pneumonia.<sup>29</sup> Significant bulbar involvement has a direct adverse effect on pulmonary health and is associated with the poorest prognosis.<sup>30</sup>

### Spinal Features

Although ALS affects chiefly the skeletal muscles of the body, leading to severe motor impairment and eventual paralysis, its most lethal effects are upon the muscles of respiration. Respiratory deterioration in ALS does not have a clear pattern of progression, but appears to occur as bulbar/spinal symptoms worsen. Three muscle groups, two of which are spinal, are essential for effective ventilation, including inspiration and expiration. The third group includes those bulbar muscles that manage the upper airway. In ALS, any or all of these mechanisms may be impaired.<sup>31</sup>

- **Loss of upper airway muscle function** may present in three ways; inability to swallow effectively, aspiration of oral pharyngeal contents, and less commonly, a variable upper airway obstruction.<sup>32</sup>
- **Weakness of inspiratory muscles** leads to loss of sigh volumes, microatelectasis, and loss of lung compliance. Decreased lung compliance increases work of breathing, resulting in a gradual weakening of the diaphragm, external intercostal muscles, and accessory muscles of respiration. The resultant discrepancy between amount of energy expended and air ventilated generates a sensation of dyspnea that may persist even at rest.<sup>33</sup>
- **Weakness of expiratory muscles** does not affect ventilation directly, but does result in loss of cough function, impairing ability to clear secretions from the lungs. Consequently, patients develop atelectasis, recurrent, increasingly refractory lower respiratory tract

infections, reduced lung compliance, and increased requirement for oxygen. The relentlessly increasing effort demanded for breathing escalates fatigue and accelerates weakening of the respiratory muscles.<sup>34</sup>

ALS is not a disease of the lungs. Nevertheless, the mechanisms of respiratory failure described above create a progressive decline in both pulmonary function and the effectiveness of the pulmonary defense system.<sup>35</sup>

## Risk Factors Compromising Pulmonary Defenses

Each of the respiratory muscle-related compromises to pulmonary function described above is associated with **risk factors** that affect airway clearance. One or more structural and/or functional defects may impede secretion clearance, predisposing to mucus hypersecretion and/or secretion retention, thereby increasing the incidence of recurrent inflammation, pneumonia, atelectasis and respiratory failure. In ALS, the susceptibility to pneumonia is extreme, and it ranks first as the proximate cause of death.<sup>36</sup>

The following risk factors are associated with ALS:

- ***Dysphagia/gastroesophageal reflux***

Dysphagia, or difficulty in swallowing, is a consequence of anatomical abnormalities or weakness of the muscles associated with swallowing. Dysphagia is a characteristic feature of ALS and worsens as bulbar function declines.<sup>37,38</sup> Gastroesophageal reflux occurs when a defective lower esophageal sphincter allows stomach contents to re-enter into the esophagus.

- ***Aspiration***

Aspiration involves the inhalation of secretions, vomitus, or foreign bodies into the lungs on inspiration. Aspiration of saliva and gastric contents introduces microorganisms into normally sterile airways. Although most individuals aspirate occasionally, pneumonia is uncommon due to the highly efficient host bronchopulmonary clearance mechanisms.<sup>39</sup> The efficiency of cough reflex, ciliary performance, integrity of interstitial lymphatics, local immunoglobulin production, and the scavenging ability of macrophages are crucial to the proper function of the body's bronchopulmonary clearance mechanism.<sup>40</sup> However, aspiration poses risk of severe, often fatal pneumonia in individuals with ALS.<sup>41</sup>

Consequences of aspiration:<sup>42,43</sup>

- Airway obstruction may follow aspiration
- Aspiration of particulate matter or large volumes of fluid may produce airway obstruction

- Chemical pneumonitis may develop after inhalation of gastric acid and other harsh compounds
- Pleuropulmonary infections ranging from simple aspiration pneumonia to necrotizing pneumonia and lung abscesses may occur following aspiration of contaminated oropharyngeal or gastric material.

- ***Restrictive lung disease***

Restrictive lung disease (RLD) is a breathing disorder resulting from impairment of the elastic properties of the lungs and chest wall and characterized by reduced lung volumes and capacities. In ALS, the reduced compliance of the chest wall combined with weakness or paralysis of the diaphragm and other inspiratory muscles reduces maximum inspiratory pressure and limits inspiratory and vital capacities.<sup>44</sup> Additionally, RLD decreases ability to take a deep breath and to generate expiratory force, thus impairing cough effectiveness.

- ***Ineffective cough***

Bronchial mucus plugging, exacerbated by weak cough function, is the chief precipitating factor of acute respiratory failure for patients with neuromuscular diseases including ALS.<sup>45</sup> Impaired cough function may relate to:

- poor coordination of the bulbar muscle, impairing closure of the glottis and the ability to build up
- poor coordination of the expiratory muscles, diminishing expulsive force and mucus shearing
- diminished inspiratory capacity secondary to diaphragm weakness or spinal deformity intrapleural pressure

- ***Immobility***

In ALS, neuromotor and neuromuscular dysfunction gradually diminish and finally prevent physical exercise. As a consequence, ALS patients cannot maintain aerobic capacity, bellows function, and lung volume, predisposing them to risks associated with inadequate secretion clearance.<sup>46</sup>

- ***Risks associated with assisted ventilation***

Serious pulmonary compromise may occur with an artificial airway.<sup>47</sup> Impaired airway clearance is both an indication for and a consequence of an artificial airway.<sup>48</sup> Retained secretions predispose to infection and encourage atelectasis and hypoxemia. When underlying airflow obstruction or neuromuscular weakness are present, work of breathing is increased dramatically. Moreover, when an artificial airway is in place, the defense mechanisms of the upper airway and normal mucociliary function are compromised. Pulmonary risks associated with endotracheal intubation and/or mechanical ventilation include:

- impaired airway clearance mechanisms secondary to

impairment of the mucociliary system,<sup>49,50</sup> impairment of the cough reflex,<sup>51</sup> and structural damage to airway tissue;<sup>52</sup>

- infection risks associated with bypassed airways;<sup>53</sup> and
- aspiration associated with placement of an artificial airway.<sup>54</sup>

## Consequences of Poor Secretion Clearance

The effects of dysphagia, chronic aspiration, ineffective cough, restrictive lung disease and immobility converge to limit ability to clear secretions from the tracheobronchial tree. Poor secretion clearance affects normal mucus function, disrupting the physical, biological, and chemical components of the pulmonary defense system. Excessive or retained secretions undergo qualitative changes that make it viscous and tenacious, infectious, and eventually injurious to healthy lung tissue. When mucus accumulates in the airways, harmful consequences ensue, including:<sup>55</sup>

- Impaired cough
- Retention of particulate matter (including pathogens)
- Activation of inflammation
- Airway obstruction, inhibiting O<sub>2</sub>/CO<sub>2</sub> exchange

### Inflammation

In healthy individuals, inflammation plays an important role in overcoming infection and restoring lung health. In those with ALS, however, microorganisms are poorly cleared, and the inflammatory mediators accumulate in increasingly high concentrations, jeopardizing the integrity of the lung parenchyma. Left unchecked, inflammatory disruptions in intercellular function progress until they result in the overproduction and subsequent retention of airway mucus, thus initiating the classic vicious cycle of pulmonary decline.<sup>56</sup>

Whether initiated by pulmonary infection or complications associated with artificial airways and/or mechanical ventilation, excessive inflammatory response is a major cause of respiratory decline in ALS. Inflammation is characterized by the presence of inflammatory cells and various inflammatory mediators, including proteases, chemo attractants, cytokines, leukotrienes, and others. The magnitude and persistence of inflammation in ALS may contribute to the development of parenchymal lung destruction and pulmonary fibrosis.

### Airway mucus: Response to inflammation

Airway mucus is a complex secretion that, together with the mucociliary transport system, serves primarily as a renewable and transportable barrier against inhaled toxic agents. Disturbances of this defense mechanism, such as those caused by chronic inflammation, lead to mucus hypersecretion and its accumulation in the airways.

Retained secretions play at least two key roles in the pathophysiology of ALS.

- Retained secretions **physically** obstruct airways, leading to:
  - Infectious exacerbations and bacterial colonization, resulting from stagnation of secretions
  - Immobilization of cilia
  - Pulmonary hyperinflation
  - Ventilation /perfusion mismatching
  - Atelectasis
  - Obstruction of airways
- Retained secretions **chemically** damage airways. Uncleared secretions contain high concentrations of cytotoxic inflammatory mediators, such as cytokines and leukotrienes, which can cause:
  - More mucus production
  - Increased recruitment of eosinophils
  - Edema
  - Bronchospasm
  - Progressive parenchymal injury and destruction
  - Destruction of cilia
  - Infectious exacerbations
  - Bacterial colonization
  - Irreversible fibrosis

## Rationale for Airway Clearance Therapy

When the mucociliary clearance system is impaired, instead of carrying away harmful matter, airway mucus is transformed into a vehicle for pulmonary destruction. In addition to the biophysical consequences of retained secretions, including airway obstruction and impaired gas exchange, the biochemical properties of inflammatory mucus are hazardous. Inflammatory mucus—characterized by neutrophil infiltration—results in increased protease activity. Significant mucus hypersecretion, impaired mucus clearance, and damage to the mucociliary apparatus results.<sup>57</sup> In addition, toxic byproducts of inflammation precipitate rheological changes in airway mucus, making it thick, tenacious, and less clearable by cough.<sup>58</sup> In the

accelerate the rate of pulmonary decline, compromise quality of life, and hasten fatal respiratory failure. Accordingly, there is a persuasive rationale for preventing prolonged contact of small and large airways with “toxic” mucus.

## **Airway clearance treatment modalities for ALS**

Patients’ individual needs vary greatly. The success of an airway clearance program depends upon a *careful evaluation* of each person’s needs, a *clear definition* of therapeutic and quality of life goals, and the application of *appropriate* airway clearance modality.

Evacuation of secretions may be accomplished by a variety of techniques and devices. However, for ALS patients who do not have the energy or lung capacity for techniques that depend on forced expiration, such as the Acapella® device, active cycle of breathing (ACT) or positive expiratory pressure (PEP) masks, options are limited. Percussion and postural drainage (P&PD), aka chest physiotherapy (CPT), and high-frequency chest wall oscillation (HFCWO), administered via The Vest™ Airway Clearance System (“The Vest”).

## **Improving outcomes for individuals with ALS**

Many respiratory complications associated with ALS are *preventable* or *treatable*.<sup>61</sup> Therapeutic strategies to treat ALS include techniques to augment cough, improve lung volumes, and support the patient with progressive ventilatory failure. Airway clearance therapy is an essential component of this treatment regimen.<sup>62</sup> Clinicians recognize that individuals with significant secretion clearance problems require an aggressive regimen of airway clearance including daily airway clearance therapy to slow the process of progressive lung disease, to preserve lung function, and to avoid or reduce the need for more aggressive therapy such as intravenous antibiotics and hospitalization.<sup>63,64</sup> Effective airway clearance therapy has

nevertheless, regardless of the pace and severity of symptoms, patients with the “best” outcomes are those who, together with their physicians and families, find ways to continue to live as fully as possible. To do so, patients must resolve to adhere to a regimen of supportive therapeutic interventions and to accept and adapt to disabilities as they evolve. This ideal is modeled eloquently in the currently popular book, *Tuesdays with Morrie*. In this true story, an elderly college professor dying of ALS accepts the moral challenge both to confront the ravages of ALS with fortitude and to make the most of his remaining time; for this man, the inevitability of death does not warrant defeatism.<sup>65</sup> Undeniably, ALS is a devastating disease and its consequences must not be minimized. Nevertheless, although ALS cannot yet be defeated, it can be treated.

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