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RESEARCH ARTICLE

Ventilatory support and respiratory infection in patients with Amyotrophic Lateral Sclerosis

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Introduction
Amyotrophic Lateral Sclerosis is a progressive neurodegenerative disease that causes significant and progressive functional loss, leading to a high degree of dependence. The disease's consequences include hypoventilation, inefficient cough, dysphagia, and malnutrition, which predispose patients to recurrent respiratory infections and reduced life expectancy. A growing number of Amyotrophic Lateral Sclerosis patients are being treated with mechanical ventilation at home. Ventilatory support can be invasive or non-invasive. Since little has been reported on the association between ventilatory support type and the incidence of pneumonia in patients with Amyotrophic Lateral Sclerosis, this study aims to evaluate the incidence density of pneumonia in Brazilian patients with Amyotrophic Lateral Sclerosis who received private home care, correlating it with ventilatory support type and comparing it with the global incidence among home care patients.

Methods
This observational retrospective cohort study analyzed the electronic medical records of patients treated between January and December 2022.

Results
A total of 91 patients with Amyotrophic Lateral Sclerosis were treated between January and December 2022 with mean age of 63.3 years. Of these 91 patients, 56 (62%) were tracheostomized. 33 (36%) developed pneumonia during the study period, of whom 20 had more than one infectious episode, totaling 69 pneumonia events. The incidence density of pneumonia among Amyotrophic Lateral Sclerosis patients was 3.1 cases/1000 patient days. A total of 56 (62%) Amyotrophic Lateral Sclerosis patients received invasive mechanical ventilation, and the incidence density of pneumonia was 4.1 cases/1000 ventilation days. The incidence density of pneumonia among Amyotrophic Lateral Sclerosis patients who received non-invasive ventilatory support was 1.6 cases/1000 non-invasive ventilation days and Amyotrophic Lateral Sclerosis patients who did not receive ventilatory support was 0.3 cases/1000 patient days.

Conclusions
Amyotrophic Lateral Sclerosis patients who receive specialized home care in Brazil often receive invasive mechanical ventilation. The modality of ventilatory support is correlated with the incidence of pneumonia, and those who receive invasive ventilatory support are more affected.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that causes significant and progressive functional loss, leading to a high degree of dependence. Although considered rare, its clinical and socioeconomic impact is great for both individuals and society[1-5]. The average life expectancy after diagnosis is approximately 3 to 5 years and varies according to phenotype, with respiratory compromise being the main cause of death[6-7] in more than 80% of diagnosed cases[8].

The disease's consequences include hypoventilation, inefficient cough, dysphagia, and malnutrition, which predispose patients to recurrent respiratory infections and reduced life expectancy[8]. Patients with bulbar involvement are more often dysphagic and have difficulty managing salivation, leading to a higher risk of aspiration pneumonia[9].

A growing number of ALS patients are being treated with mechanical ventilation at home[10-12]. Ventilatory support can be invasive, through a tracheostomy cannula, or non-invasive, through a facial, nasal, or oral interface. The decision to use invasive or non-invasive ventilation is shared between the patient, family, and medical team. The literature reports that 2%-15%[13-15] of ALS patients receive a tracheostomy and that this procedure is frequently used in moments of acute respiratory distress[16].

As respiratory support for patients with non-bulbar ALS, non-invasive ventilation has resulted in better survival and quality of life than invasive ventilation. Good adherence to ventilatory therapy has a positive impact on forced vital capacity and survival[17-19]. However, certain situations can hinder the use of non-invasive ventilation, such as excessive sialorrhea, discomfort and/or pressure injuries from the interface equipment, viscous bronchial secretions, and inability to manage or adapt to the interface conditions by the technical team/family members[20-22].

Invasive ventilation provides better lower airway protection against aspiration processes and helps eliminate bronchial secretions, although it may incur an increased risk of health care-related pneumonia and other complications, such as barotrauma, tracheal injuries, weaning failure, and greater ventilator dependence[8].

Although studies report that non-invasive ventilatory support leads to greater survival for patients with non-bulbar ALS than invasive ventilation[23-25], no survival improvement has been observed in patients with bulbar ALS[24-26].

Since little has been reported on the association between ventilatory support type and the incidence of pneumonia in patients with ALS, this study aims to evaluate the incidence density of pneumonia in Brazilian patients with ALS who received private home care, correlating it with ventilatory support type and comparing it with the global incidence among home care patients.

Methods

This observational retrospective cohort study analyzed the electronic medical records of patients treated between January and December 2022.

We calculated the following: 1) the incidence density of pneumonia in ALS patients (ie, the absolute number of pneumonia cases among ALS patients/number of patient days x 1000; 2) the incidence density of pneumonia associated with invasive mechanical ventilation among ALS patients (ie, the absolute number of pneumonia cases associated with invasive mechanical ventilation among ALS patients/number of mechanical ventilation days x 1000); 3) the incidence density of non-invasive mechanical ventilation-associated pneumonia cases among ALS patients (ie, the absolute number of pneumonia cases among ALS patients who received non-invasive mechanical ventilation/number of non-invasive mechanical ventilation days x 1000; 4) the incidence density of pneumonia in ALS patients who did not receive ventilatory support (ie, the absolute number of pneumonia cases among ALS patients who did not receive ventilatory support/patient days x 1000; 5) the incidence density of pneumonia among all patients (ie, the absolute number of pneumonia cases/number of patient days x 1000; 6) the incidence density of mechanical ventilation-associated pneumonia among all patients (ie, the absolute number of mechanical ventilation-associated pneumonia cases/number of mechanical ventilation days x 1000.

Institutionally-defined diagnostic criteria were used to identify infections based on ANVISA [33] and the U.S. Centers for Disease Control [34] protocols, as detailed in Table 1. Clinically indicated cases of pneumonia were also considered, regardless of the aforementioned epidemiological criteria.

Table 1 – Diagnostic criteria for pneumonia

Criterion 1	Thorax X-ray demonstrating pneumonia or presence of new pulmonary infiltrate, opacification, or cavitation **AND** at least **one** of the following respiratory changes: fever, recent onset cough or cough worsening; sputum or chronic sputum worsening; pleuritic chest pain; altered respiratory auscultation or recently worsened auscultation (rattling, snores, wheezing or bronchophony); increased respiratory rate (≥ 25 per minutes); O2 saturation < 94% in room air or a reduced baseline O2 saturation > 3%.
Criterion 2	At least **one** of the following signs and symptoms: Fever without any other known cause; leukopenia or leukocytosis **AND** at least **one** of the following: Occurrence of purulent secretion or change of secretion characteristics or increased secretion or increased need of aspiration; gas exchange worsening (worsening of ratio PAO2/FIO2 or increased need of oxygen or increased ventilator parameters).
Criterion 3	Patient with underlying disease with two X-rays demonstrating **one** of the following findings: New, progressive, and persistent infiltrate; opacification; cavitation.
Criterion 4	Patient has at least **two** of the following signs and symptoms: Fever, cough; occurrence or usual increase of secretion; wheezing.

The results are presented as number (n), frequency (%), and mean or median values, and were compared using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

Results

A total of 91 patients with ALS were treated between January and December 2022, of whom 54% were male and 60% were older adults (mean age of 63.3 years).

Of these 91 patients, 56 (62%) were tracheostomized. Regarding ventilatory support, 61 (67%) received continuous ventilatory support, 15 (16.5%) received intermittent ventilatory support, and 15 (16.5%) received no ventilatory support during the study period.

The ventilatory support profile according to type (invasive vs non-invasive) and time of use is shown in Table 2.

Of the 91 patients, 33 (36%) developed pneumonia during the study period, of whom 20 had more than one infectious episode, totaling 69 pneumonia events. The incidence density of pneumonia among ALS patients was 3.1 cases/1000 patient days. The incidence density of pneumonia among home care patients, regardless of the baseline diagnosis, was 1.2 cases/1000 patient days.

A total of 56 (62%) ALS patients received invasive mechanical ventilation, and the incidence density of pneumonia was 4.1 cases/1000 ventilation days, corresponding to 62 cases of pneumonia during the study period. The incidence density of pneumonia among ALS patients who received non-invasive ventilatory support was 1.6 cases/1000 non-invasive ventilation days, with 6 cases of pneumonia in this group. Only 1 case of pneumonia occurred in ALS patients who did not receive ventilatory support (0.3 cases/1000 patient days). The incidence of pneumonia in the invasive mechanical ventilation group was significantly higher than in the non-invasive ventilation group ($p = 0.002$) and the group without ventilatory support ($p < 0.001$). There was no significant difference between the non-invasive group and the group without ventilatory support ($p = 0.44$) (see Table 3).

Table 2 – Clinical profile of patients with amyotrophic lateral sclerosis

	Total 91 (100%)	Invasive Ventilation 56 (62%)	Non-invasive Ventilation 20 (22%)	No ventilation support 15 (16%)
Gender				
Female	42 (46%)	26 (62%)	9 (21%)	7 (17%)
Male	49 (54%)	30 (61%)	11 (22%)	8 (16%)
Age				
Years (median ± SD)	63,4	63,03	62,65	65,86
Ventilation Lengh				
Intermitente	15 (20%)	1 (7%)	14 (93%)	0
Continuos	61 (80%)	55 (90%)	6 (10%)	0
Age Group				
Pediatrics	0	0	0	0
Adults	37 (41%)	23 (62%)	9 (24%)	5 (14%)
Eldery	54 (59%)	33 (61%)	11 (20%)	10 (18%)

Table 3 – Pneumonia and ventilatory support in patients with amyotrophic lateral sclerosis

	IMV n = 56	NIMV n = 20	p value *	SV n = 15	p value **
Patients with respiratory infection, n(%)	28 (50%)	3 (15%)	**0,008** +	1 (7%)	**0,003** +
Incidence density, cases per 1000 patient days	4.2	1.6	**0,003** ++	0.3	**< 0,001** ++

IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; SV: spontaneous ventilation. *Comparison between IMV and NIMV; ** comparison between IMV and SV; +Fisher's exact test; ++Mann-Whitney test

The incidence density of mechanical ventilation-associated pneumonia among patients in home care, regardless of baseline diagnosis, was 3.9 cases/1000 patient days.

Discussion

In ALS, loss of respiratory function is the main marker of survival and quality of life, and respiratory dysfunction is associated with infectious pulmonary complications, the main cause of death [35].

Our results indicate that the incidence density of pneumonia among ALS patients was higher than among the general population in home care (3.0 vs 1.2 cases/1000 patient days). This is compatible with a direct correlation between the pathophysiology of ALS and respiratory infections, unlike other pathologies treated at home, such as cardiovascular diseases, skin wounds, etc.

The literature reports that tracheostomy and invasive ventilation rates in ALS patients are < 15%[13-15]. The choice to perform a tracheostomy depends on cultural, social, and clinical factors regarding criteria such as the speed of disease progression and the presence of bulbar involvement. Although tracheostomy ventilation can prolong survival for many years [26,27], it requires significant financial resources and may not correlate with good quality of life, resulting in high dependency and caregiver burden [26,28,29]. Tracheostomies are not encouraged in Europe and North America[30-32], but are still common practice in low- and middle-income countries like Brazil, as evidenced by the 61% of patients with tracheostomy in the present study.

The correlation analysis between ALS and ventilatory support type showed a significant relationship between invasive ventilatory support and the incidence of pneumonia (invasive vs. non-invasive, $p = 0.002$; invasive vs. no ventilatory support, $p < 0.001$). There was no significant difference between the non-invasive and no ventilatory support groups ($p = 0.44$). Although the study was limited by not analyzing additional data that could be related to respiratory infections, such as bulbar involvement or the degree of respiratory function impairment, the findings lend biological plausibility to the idea that patients with ALS who receive invasive ventilatory support (tracheostomy) are more susceptible to respiratory infections than those who receive non-invasive support. This point should be considered when deciding about the best type of ventilatory support to use.

Among the subgroup of patients with non-invasive or no ventilatory support, there was a low incidence density of pneumonia (1.6 and 0.3 cases/1000 patient days), which is compatible with the literature. Over a 15-year follow-up period, Sorenson et al[36]. reported the incidence of aspiration pneumonia was 1.7 cases/100,000 person years in a population of 40 patients. The same authors reported similar results among ALS patients between 1925 and 1998 [37], with only 18% of patients receiving non-invasive ventilatory support. None of these studies correlated ventilatory support type with infection incidence in ALS.

According to Sorenson et al.[36], ALS patients on mechanical ventilation have a higher incidence of respiratory infection than those on ventilatory support for other pathologies. Conversely, ALS patients on invasive ventilation in the present study had a similar incidence of pneumonia to patients on invasive ventilation due to other diagnoses (4.1 vs. 3.9 episodes/1000 ventilation days). The main hypothesis for this finding is that the clinical complexity of other home care patients on invasive ventilation was also high, similar to that of patients with ALS, including pediatric patients with neuromuscular diseases, such as spinal amyotrophy, in which the same pathophysiological correlation with pneumonia is expected.

Zakharova et al.[9] report that multiple factors are associated with the aggressiveness of the disease and the prognosis, principally age and

comorbidities at diagnosis, malnutrition, bulbar involvement, the speed of evolution, the type of presentation (involvement of lower or upper motor neurons) and reduced forced vital capacity. The fact that 56 (62%) patients had a tracheostomy, 55 of whom were on continuous ventilation, allows us to infer that the respiratory systems of these patients were highly compromised, which is compatible with the health care situation in Brazil, since the diagnosis it often late and only the most complex patients, who have more severe and advanced diseases, are referred for invasive ventilatory support in home care. However, our study was limited by not evaluating clinical parameters such as bulbar involvement and the degree of respiratory dysfunction, which could be correlated with pneumonia in this population.

Conclusions

Among Brazilian home care patients, those with ALS had a higher incidence of pneumonia than those with other pathologies.

Amyotrophic Lateral Sclerosis patients who receive specialized home care in Brazil often receive invasive mechanical ventilation. The modality of ventilatory support is correlated with the incidence of pneumonia, and those who receive invasive ventilatory support are more affected.

Studies correlating pneumonia and ventilatory support should include additional clinical data, such as malnutrition, dysphagia, and forced vital capacity for a broader understanding of the subject.

Declaration of conflict of interest

I, Fabiana Schimidt Cezar, author responsible for submitting the manuscript entitled Ventilatory support and respiratory infection in patients with Amyotrophic Lateral Sclerosis, and all the co-authors presented here, declare that we have no conflict of interest.

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