



Major approaches to nutrological management and gut microbiota in neurodegenerative diseases and brain injuries: a systematic review

Sylvia Renata Lannes Magalhães^{1,*}

¹ Federal University of Espírito Santo, Espírito Santo, Brazil.

*Corresponding author: Dr. Sylvia Renata Lannes Magalhães.

Federal University of Espírito Santo, Espírito Santo, Brazil.

E-mail: dra.sylviamagalhaes@gmail.com

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Abstract

Introduction: The prevalence of neurodegenerative diseases and dementia, such as Alzheimer's disease (AD), is increasing. However, the currently available symptomatic and disease-modifying therapies have shown limited benefits for neurodegenerative diseases in clinical settings. **Objective:** It was to carry out a systematic review to externalize and discuss the main findings on the effects of enteral nutritional therapy, as well as on the action of the intestinal microbiota in patients with brain injuries or neurodegenerative diseases. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from May to June 2026 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 122 articles were found, and 31 articles were evaluated in full, and 28 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with $X^2=71.9\%>50\%$. It was concluded that probiotic-supplemented enteral nutrition effectively reduces the risk of mortality, gastrointestinal complications, and infection, and shortens ICU length of stay; therefore, it should be widely adopted for the management of these patients. Nasal inspiratory pressure during a sniff at baseline is an early indicator of disease progression and, consequently, of the need for enteral nutrition in amyotrophic lateral sclerosis. Furthermore, issues regarding tolerance, diarrhea, and

abdominal distension decreased between the 3- and 6-month follow-ups in patients receiving home enteral nutrition.

Keywords: Nutrological therapy. Nutrients. Gut microbiota. Neurodegenerative disease.

Introduction

The prevalence of neurodegenerative diseases and dementia, such as Alzheimer's disease (AD), is rising. However, currently available symptomatic and disease-modifying therapies have shown limited benefits for neurodegenerative diseases in clinical settings. Halting the progression of neurodegeneration and cognitive decline—or even improving impaired cognition and function—are the clinically relevant goals of treatments for neurodegenerative diseases. Aging is the primary risk factor for neurodegenerative diseases and their associated comorbidities, such as vascular pathologies, in the elderly population [1].

Critically ill patients with brain injuries or severe neurodegenerative diseases, such as amyotrophic lateral sclerosis, are at increased risk of malnutrition due to complex issues and the deleterious effects of these diseases on protein and energy metabolism; this leads to metabolic dysregulation, a hypercatabolic state, and the depletion of energy reserves [1-3].

Providing adequate and timely nutritional support to critically ill patients is therefore considered crucial [4,5], given that protein deficiency and energy depletion in severely ill individuals have been linked to adverse health outcomes—including infections and increased mortality—as well as longer intensive care unit (ICU) stays and higher costs [4,6-10].

For instance, the incidence of malnutrition in stroke patients ranges from 6.1% to 62.0%, depending on the method and timing of the nutritional assessment [11,12], while dysphagia was evident in approximately 50% of patients during the acute phase [13-15]. Nutritional status is closely linked to the long-term clinical course of stroke patients; malnutrition is associated with an increased risk of post-stroke infection, recurrent stroke, and mortality [12,16-18].

In this regard, enteral nutrition via the gastrointestinal tract is considered the first-choice nutritional support and a quality-of-care indicator for critically ill patients [1,2], as it helps preserve intestinal mucosal integrity and reduce infection, morbidity, and mortality. However, providing adequate nutritional support to critically ill patients remain a challenge due to the impact of the underlying diagnosis and concomitant treatments on nutritional status [2].

Against this backdrop, fortifying enteral formulas with prebiotics can improve the adequacy of nutritional therapy by enabling specific changes in the composition and/or function of the gastrointestinal microbiota that benefit the host [1]. Fructooligosaccharide prebiotics selectively stimulate the proliferation of bifidobacteria—and potentially lactobacilli—while providing a substrate for fermentation and the production of short-chain fatty acids (SCFAs) [19,20].

Although the effect of fructooligosaccharides on colonic microbiota has been extensively studied in healthy populations, few clinical trials have investigated their use in enteral formulas; however, existing studies suggest that fructooligosaccharide content may help stabilize intestinal barrier homeostasis and reduce infection rates [1,19]. Consequently, some clinical studies have explored the effect of probiotic-supplemented enteral nutrition on the clinical course of patients with brain injuries or neurodegenerative diseases, observing that early enteral nutrition with probiotics can improve intestinal homeostasis in these patients, thereby enhancing other clinical outcomes [1,19,20].

Therefore, this study aimed to conduct a systematic review to present and discuss key findings on the effects of nutritional therapy and the role of the gut microbiota in patients with neurodegenerative diseases.

Methods

Study Design

This study followed an international systematic review model, adhering to PRISMA (Preferred

Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>.

Accessed on: June 7, 2026. It also followed the AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) standards for methodological quality. Available at: <https://amstar.ca/>. Accessed on: June 7, 2026.

Data Sources and Search Strategy

The literature search process was conducted from May to June 2026 using Web of Science, Scopus, PubMed, LILACS, EBSCO, SciELO, and Google Scholar, covering scientific articles published from various periods up to the present. The following descriptors (DeCS/MeSH terms) were used: "Nutrological therapy," "Nutrients," "Gut microbiota," and "Neurodegenerative diseases," employing the Boolean operator "AND" between MeSH terms and "OR" between the search terms.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on risk of bias, clarity of comparisons, precision, and consistency of analyses. Priority was given to systematic reviews or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, in accordance with the GRADE instrument. Risk of bias was analyzed using the Cochrane tool via funnel plot analysis (sample size versus effect size) and Cohen's d test.

Results and discussion

Summary of Findings

A total of 122 articles were identified and subjected to an eligibility assessment; 28 studies were ultimately selected for inclusion in this systematic review. The selected studies demonstrated moderate to high quality (Figure 1), based on the level of scientific evidence from study designs such as meta-analyses, consensus statements, and randomized clinical, prospective, and observational trials. Biases did not compromise the scientific foundation of the studies. According to the GRADE instrument, the majority of studies showed homogeneity in their results ($X^2 = 71.9\% > 50\%$). Based on the Cochrane risk-of-bias tool, the overall assessment identified 25 studies with a high risk of bias and 21 studies that did not meet the GRADE and AMSTAR-2 criteria.

Articles in systematic review (n=28)

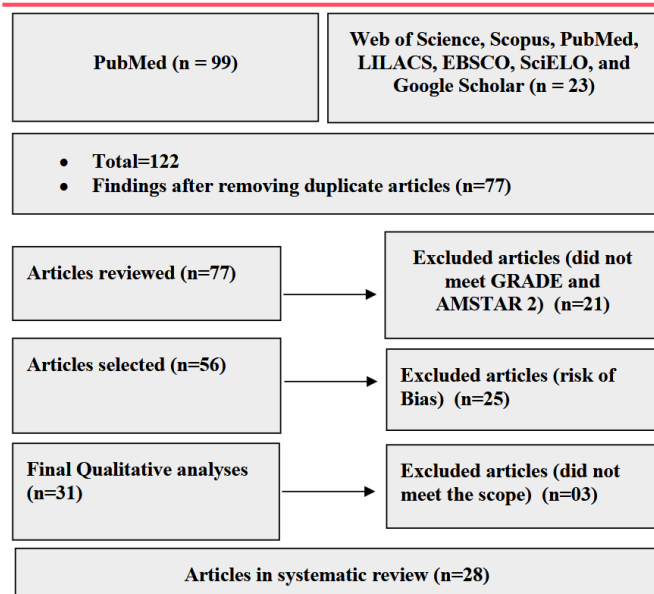


Figure 1. Selection of articles. Source: Own authorship.

Figure 2 presents the results regarding the risk of bias across the studies using a funnel plot, showing the calculation of effect size (magnitude of difference) via Cohen's d. Precision (sample size) was determined indirectly as the inverse of the standard error ($1/\text{Standard Error}$). The plot exhibited a symmetrical pattern, suggesting no significant risk of bias among either studies with small sample sizes (lower precision), shown at the base of the plot, or studies with large sample sizes, shown at the top.

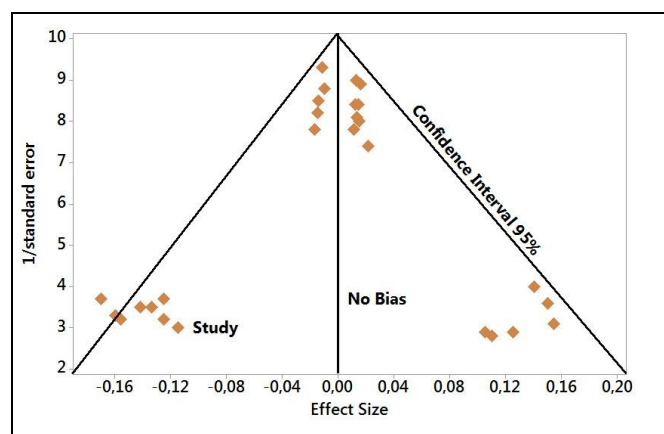


Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small-sample-size studies shown at the bottom of the plot. Studies with high confidence and strong recommendations are shown at the top of the plot (n = 28 studies). Source: Own authorship.

Major Results – Nutrological Modulation in Neurodegenerative Diseases

Based on the literature selected for this study, it is evident that gut microbiota metabolites can be important for host health; however, few studies have investigated the correlation between the human gut

microbiome, fecal metabolite production, and their impact on the plasma metabolome. Omnivorous and vegan diets can alter fecal amino acid levels, supporting the growth of Firmicutes capable of amino acid metabolism. Furthermore, the impact of enteral nutritional therapy—particularly the role of fiber—on the human microbiome influences metabolites that can affect health [21].

In this context, Du et al. (2020) [22] conducted a meta-analysis to determine whether early enteral nutrition with probiotics could reduce mortality and infection rates in patients with severe traumatic brain injury, improve gastrointestinal function, and shorten the length of stay in the intensive care unit (ICU). A total of 39 studies involving 3,387 patients were included. Early enteral nutrition supplemented with probiotics was associated with a reduced risk of infection (pooled risk ratio [RR], 0.486; 95% confidence interval [CI], 0.394–0.599), a reduced risk of mortality at 7, 14, and 28 days (pooled RRs: 0.415, 0.497, and 0.385; 95% CIs: 0.196–0.878, 0.297–0.833, and 0.197–0.751, respectively), and a reduced risk of gastrointestinal complications (pooled RR, 0.363; 95% CI, 0.274–0.481). It also shortened the time to recovery of enteral function, as well as the length of hospital and ICU stays (standardized mean differences: -3.327 and -1.461; 95% CIs: -6.213 to -0.440 and -2.111 to -0.811, respectively).

Tian et al. (2022) [23] demonstrated that the gut microbiome of stroke patients is significantly altered and that the degree of microbiota disturbance correlates with prognosis. Enteral nutrition can remodel the gut microbiome and is important for stroke patients with dysphagia. A total of 17 healthy controls (HC), 54 stroke patients receiving oral feeding (OF), and 50 stroke patients receiving enteral nutrition were matched to investigate alterations in gut microbiota associated with enteral nutrition during the first week after admission, as well as dynamic changes. The relationship between the gut microbiome and clinical characteristics was investigated in a larger sample of participants receiving enteral nutrition (n=147). Survival analysis was performed using Cox proportional hazards regression. Gut microbiota composition and structure were analyzed via 16S rRNA sequencing. Compared to the HC and AO groups, patients receiving enteral nutrition exhibited significantly different gut microbiota compositions at weeks 1 and 2. Thus, the gut microbiota in ischemic stroke patients receiving enteral nutrition is significantly altered, and specific bacterial strains may be associated with prognosis and clinical indicators.

A randomized clinical study compared the use of standard enteral formula versus enteral formula with

prebiotic content regarding nutritional therapy outcomes among patients in neurocritical care. Forty-six adult patients in neurocritical care were included; they received nutritional therapy with either standard enteral formula (SEF group; $n=23$) or enteral formula with prebiotic content (EFPC group; $n=23$) during their ICU stay. Data on patient demographics (age, sex), diagnosis, comorbidities, anthropometry, hospital and ICU length of stay (LOS), Nutritional Risk Screening (NRS-2002) score, and Acute Physiology and Chronic Health Evaluation (APACHE-II) score were recorded at enrollment. Data on daily nutritional intake, laboratory findings, complications, and pharmacological treatments were recorded on Days 1, 4, 7, 14, and 21 of nutritional therapy in both the SEF and EFPC groups. Compared to SEF, the use of EFPC was associated with significantly higher values for total energy, carbohydrates, proteins, lipids, enteral volume, and fluid intake (p -values ranging from <0.05 to <0.001) on each day of nutritional therapy. The target dose was achieved by the majority of patients (86.9%), and for most patients (71.7%), this occurred by the 4th day of nutritional therapy within the overall study population. Patients in the EFPC group showed a non-significant trend toward a higher (95.7% vs. 78.3%) and earlier (87.0% vs. 56.5% on day 4) rate of achieving the target dose, a lower rate (8.7% vs. 56.5%) and faster improvement (none vs. 52.2% had diarrhea on day 7) of diarrhea, and a lower need for insulin (56.5% vs. 13.0%, $p = 0.002$). Nutritional therapy was associated with a significant decrease in prealbumin (Day 14 vs. Day 1, $p < 0.05$ for both), albumin (Day 14 vs. Day 1, $p < 0.01$ for SEF, $p < 0.05$ for PFE), hemoglobin (Day 14 and Day 21 vs. Day 1 and Day 14 vs. Day 4, $p < 0.001$ for each in the SEF group; Day 7, Day 14, and Day 21 vs. Day 1, $p < 0.01$ for each in the PEF group), and hematocrit (Day 14 and Day 21 vs. Day 1, $p < 0.001$ for each in both the SEF and EFPC groups). Thus, the findings revealed that the target nutritional intake was achieved in the majority of neurocritical patients through nutritional therapy; meanwhile, EFPC was associated with a non-significant trend toward more frequent and earlier achievement of the target dose, along with a significantly lower rate and faster resolution of diarrhea compared to the SEF group. Prealbumin and albumin levels remained below the normal range, while C-reactive protein (CRP) and white blood cell (leukocyte) counts remained above the normal range throughout the nutrition period in both groups; creatinine and urea levels were higher in the EFPC group than in the SEF group [24].

Furthermore, maintaining adequate nutrition is crucial for people with ALS. Enteral tube feeding is

offered to individuals with difficulty swallowing (dysphagia) to prevent weight loss and aspiration pneumonia. Among the types of enteral tube feeding, percutaneous endoscopic gastrostomy (PEG) is the standard procedure. ...offered to patients with ALS. Thus, Sulistyo et al. (2023) [25] evaluated the efficacy of PEG or other forms of enteral tube feeding in patients with ALS, compared to oral feeding without enteral tube feeding. No randomized clinical trials were found indicating whether enteral tube feeding is effective compared to continuing oral feeding for any of the outcome measures.

Other authors investigated, via a retrospective study, the role of baseline sniff nasal inspiratory pressure (SNIP) in predicting PEG placement in ALS. Data were included from a clinical incident cohort of 179 ALS cases treated at a multidisciplinary ALS unit. At baseline, patients underwent detailed neurological, nutritional, and respiratory assessments, including measurements of SNIP and forced vital capacity. Patients were subsequently followed up approximately every three to six months for as long as they could attend the center. During the follow-up period, 75 participants (42%) underwent PEG placement. PEG placement was more frequent (57% vs. 31%; $p = 0.001$) and occurred earlier (11.6 ± 14.0 months after the first consultation vs. 23.3 ± 15.5 months; $p < 0.0001$) in the group of patients with a baseline SNIP ≤ 40 cm H₂O. Baseline SNIP was a predictor of PEG placement even after adjustment for multiple potential confounders (HR 0.98; 95% CI: 0.96–0.99; $p = 0.02$) [26].

In this regard, symptoms such as dysphagia, depression, cognitive impairment, difficulty with self-feeding and meal preparation, hypermetabolism, anxiety, respiratory insufficiency, and fatigue during meals increase the risk of malnutrition in patients with ALS. Malnutrition negatively affects prognosis and quality of life, making early and frequent nutritional assessments and interventions essential. Implementing an appropriate caloric diet, modifying food texture, using adaptive eating utensils, and placing a feeding tube help prevent malnutrition. When nutritional status is compromised by dysphagia and weight loss (5%–10% of usual body weight) or a body mass index <20 kg/m² without weight loss, and when forced vital capacity is $>50\%$, placement of a percutaneous endoscopic gastrostomy tube is indicated. When forced vital capacity is $<50\%$, a radiologically inserted gastrostomy is the preferred method for enteral access due to lower risks of aspiration and respiratory complications. Parenteral nutrition is indicated only when enteral nutrition is contraindicated or impossible [27].

Finally, home enteral nutrition (HEN) is used to prevent or correct malnutrition in outpatients. A prospective, observational, multicenter study was conducted across 21 Spanish hospitals. The study included patients receiving HEN via nasogastric tube or ostomy; a total of 414 patients were enrolled. The majority of diagnosed conditions were neurodegenerative diseases (64.8%). A total of 100 patients (25.3%) had diabetes. Mean weight was 59.3 ± 10.4 kg, and mean BMI was 22.6 ± 3.2 kg/m². Moderate protein-energy malnutrition was the most common status at baseline (46.4%). Improvement in nutritional status at six months was observed in over 75% of patients ($p < 0.05$). Issues regarding tolerance, diarrhea, and abdominal distension decreased between the 3-month and 6-month follow-up visits ($p < 0.05$). Patients who received intermittent enteral nutrition experienced fewer tolerance-related effects (OR 0.042; 95% CI 0.006–0.279) and less diarrhea (OR 0.042; 95% CI 0.006–0.279) [28].

Conclusion

It was concluded that probiotic-supplemented enteral nutrition effectively reduces the risk of mortality, gastrointestinal complications, and infection, and shortens ICU length of stay; therefore, it should be widely adopted for the management of these patients. Nasal inspiratory pressure during a sniff at baseline is an early indicator of disease progression and, consequently, of the need for enteral nutrition in amyotrophic lateral sclerosis. Furthermore, issues regarding tolerance, diarrhea, and abdominal distension decreased between the 3- and 6-month follow-ups in patients receiving home enteral nutrition.

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Author contribution: **Conceptualization; Data curation; Formal Analysis; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing-review & editing-** Sylvia Renata Lannes Magalhães.

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Application of Artificial Intelligence (AI)

Not applicable.

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It was performed.

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