ESPEN guideline clinical nutrition in neurology

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SUMMARY

Neurological diseases are frequently associated with swallowing disorders and malnutrition. Moreover, patients with neurological diseases are at increased risk of micronutrient deficiency and dehydration. On the other hand, nutritional factors may be involved in the pathogenesis of neurological diseases.

Multiple causes for the development of malnutrition in patients with neurological diseases are known including oropharyngeal dysphagia, impaired consciousness, perception deficits, cognitive dysfunction, and increased needs.

The present evidence- and consensus-based guideline addresses clinical questions on best medical nutrition therapy in patients with neurological diseases. Among them, management of oropharyngeal dysphagia plays a pivotal role. The guideline has been written by a multidisciplinary team and offers 88 recommendations for use in clinical practice for amyotrophic lateral sclerosis, Parkinson’s disease, stroke and multiple sclerosis.

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1. Introduction

Numerous neurological diseases demonstrate a major impact on nutrition and the nutritional state of affected patients. In addition to paralysis, immobility, abnormal motor function and various neuropsychological disturbances, it is oropharyngeal dysphagia that exerts the most profound impact on nutritional intake. For the purpose of this guideline, those conditions with the highest prevalence rates, frequent involvement of dysphagia and malnutrition were chosen. Also, we have considered the conditions in which clinical issues about medical nutrition therapy arise that can be a matter of debate. These are amyotrophic lateral sclerosis (ALS), Parkinson’s disease, stroke and multiple sclerosis (MS). To enhance the generalizability of the guideline, a chapter about oropharyngeal dysphagia in general is included as this is a common feature of many neurological disorders.
Especially in rare neurological diseases, the impact of nutritional issues has not been extensively investigated. However, especially if dysphagia is present in these conditions, there is much concern about how to feed the patient and how to stabilize the nutritional state. Thus, data from common diseases have to be cautiously translated to this field.

The oropharyngeal swallow involves a rapid, highly coordinated set of neuromuscular actions beginning with lip closure and terminating with opening of the upper esophageal sphincter. The central coordination of this complex semiautomatic sensorimotor task uses a widespread network of cortical, subcortical and brainstem structures. Many diseases and disorders affecting the central swallowing network or downstream peripheral nerves, muscles and structures may result in an impaired oropharyngeal swallow, i.e. oropharyngeal dysphagia (OD). In addition, aging is also associated with multifactorial changes of swallowing physiology for which the term presbyphagia has been coined. OD broadly affects respiratory safety due to the increased risk of aspiration, and swallowing efficacy leading to the impeding danger of insufficient nutrition and hydration [1]. Within the ICD 10 catalogue, dysphagia is referenced with the code R13. More specific, R13.0 denominates the inability to swallow at all, R13.11 stands for oral phase dysphagia, R13.12 for oropharyngeal dysphagia and R13.13 for pharyngeal dysphagia.

OD is one of the most frequent and life-threatening symptoms of neurological disorders [2]. Swallowing impairment is observed in at least 50% of patients with ischemic or hemorrhagic stroke [3–5]. These patients have a three-fold increased risk of developing early aspiration pneumonia, and their mortality is significantly higher than in non-dysphagic stroke patients [4]. Similar data have been published for severe traumatic brain injury, in which the incidence of clinically relevant dysphagia is approximately 60% [6]. In this patient population, the occurrence of dysphagia is associated with significantly longer artificial respiration and prolonged artificial nutrition [7]. In patients with Parkinson’s disease, neurogenic dysphagia is also a major risk factor for the development of pneumonia, the most frequent cause of death in this patient group [8]. In addition, swallowing disorders in these patients typically lead to major and long-term reduction in quality of life (QoL), insufficient medication intake and pronounced malnutrition [9]. In multiple sclerosis, dysphagia occurs in more than one third of patients [10] and increases the risk for aspiration pneumonia and death in particular in the late stages of the disease [11]. Up to 30% of all ALS patients present with swallowing impairment at diagnosis [12] and practically all ALS patients develop dysphagia as the disease progresses. In 15% of all cases, myasthenia gravis manifests itself with swallowing impairment. As the illness progresses, over 50% of all patients are affected, and in more than 50% of cases, a myasthenic crisis is preceded by dysphagia [13]. Patients with inflammatory muscle disorders are also often subject to swallowing impairment. The frequency is approximately 20% in dermatomyositis, 30–60% in polymyositis, and between 65 and 86% in inclusion body myositis [14]. Finally, dysphagia also represents an important diagnostic and therapeutic challenge in the intensive care unit. Regardless of the primary illness, 70–80% of patients requiring prolonged mechanical ventilation present, at least temporarily, with significant swallowing impairment and aspiration after weaning from artificial respiration, predominantly due to a critical illness polyneuropathy [15]. This impairment not only necessitates prolonged artificial nutrition, but is also linked to serious complications, such as pneumonia and the necessity for reintubation. In addition, it is an independent predictor of increased mortality [16]. Apart from these specific disorders, increasing age itself is a well-established risk factor for OD. The prevalence of this condition among independently living older persons is 16% in the 70–79-year old group and 33% in the ≥80-year old group. Furthermore, 51% of institutionalized older persons are affected and up to 47% of frail elderly patients hospitalized for acute illness are diagnosed with OD. Consequences of OD in the elderly are devastating and include aspiration pneumonia, dehydration and malnutrition [17].

2. Methodology

2.1. Methodology of guideline development

The guideline was developed by an expert group of the disciplines: Clinical nutrition, Neurology, Geriatrics, Dietetics and Intensive Care, from 9 countries. All members of the working group had declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE).

Based on the standard operating procedures for ESPEN guidelines and consensus paper [18] we decided on topics to be covered at the start of the guideline process through several rounds of discussion and modification. Initially, the guideline was focused on chronic neurological diseases including ALS, PD and MD, but after a meeting in September 2014, we decided to broaden the scope of the guideline and to include stroke, in order to address the main neurological diseases. To initiate the literature searches, we designed 41 specific clinical questions, in a PICO format when appropriate. The working process was supervised and monitored by the ESPEN Guideline office for methodological quality. On the internet portal www.guideline-services.com, the draft and the literature was accessible at any time exclusively for members of the working group. After the literature search, evaluation and grading of the evidence, the guideline development group drafted a total of 88 recommendations. The draft was send to the ESPEN members via email in a first Delphi round in July 2016. We received a strong consensus (agreement of >90%) in 91.8% of recommendations, consensus (agreement of 75–90%) in 8.1% of recommendations. None of the recommendations reached an agreement lower than 75%. The recommendations with an agreement lower than 90% were discussed in an ESPEN guidelines consensus conference, which was performed on September 18th during ESPEN Congress 2016 in Copenhagen. After the voting, all the selected recommendations were discussed; modifications were included, and reached a consensus greater than 85%.

2.2. Search strategy

Before starting with the classical literature search, we explored and identified relevant published valid guidelines (German Guidelines-DGEM, NICE, SIGN …). After this first review, we searched the main Bibliographic Databases (Pubmed, EMBASE, and the Cochrane Library) for recent systematic reviews and meta-analyses that answered our clinical questions. In their absence, we looked for other indirect systematic reviews and meta-analyses and, in the absence of these, we looked for comparative studies, whether randomized or not. Also an updated literature search was conducted to retrieve further comparative studies. The screening was performed by reading the abstract, followed by the entire article when necessary. Literature search was conducted for the last 10 years, until June 2016, although the working group was allowed to consult some highly relevant previous articles. Due to the complexity of the literature search for all the questions assessed, we show an example of the search strategy for the clinical question 35 (Table 1). The classification of the literature according to evidence levels and the grades and forms of recommendation were performed
following the Scottish Intercollegiate Guidelines Network (SIGN) grading system [22], updated in 2014 (Tables 2 and 3).

Some of the recommendations of these guidelines were developed on the basis of expert opinion because we found no evidence or only low quality evidence in the literature.

In case of inconsistent data between different studies regarding one clinical question, a consensus within the group was achieved. The manuscript was reviewed and align with the recent ESPEN Guidelines on definitions and terminology in clinical nutrition [23].

3. Amyotrophic lateral sclerosis (ALS)

ALS is a complex neurodegenerative disorder characterized by progressive loss of motor neurons, resulting in progressive atrophy of skeletal muscles, including the respiratory muscles. The etiology of ALS is multifactorial. Increased oxidative stress, glutamate toxicity, mitochondrial dysfunction, inflammation and apoptosis have been implicated as causative factors in neuronal insult that initiated the pathogenesis of the disease [24]. In ALS patients, malnutrition is common. The following factors has been associated with the risk of malnutrition [25]:

- The degeneration of bulbar neurons manifests as difficulty in chewing, oral preparation, time required to complete a meal, and dysphagia.

Table 3
Grades and forms of recommendations (SIGN grading system) [22].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>A</td>
<td>Strong recommendation for use restricted to trials</td>
</tr>
<tr>
<td>B</td>
<td>Conditional recommendation for use restricted to trials</td>
</tr>
<tr>
<td>C</td>
<td>Conditional recommendation for research and possibly conditional recommendation for use restricted to trials</td>
</tr>
<tr>
<td>D</td>
<td>Strong recommendation against</td>
</tr>
<tr>
<td>E</td>
<td>Strong recommendation for</td>
</tr>
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Table 2
Levels of evidence (SIGN grading system) [22].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>−</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>+++</td>
<td>High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>+ +</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>−</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>-</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>0</td>
<td>Expert opinion</td>
</tr>
</tbody>
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- Anorexia is common; it is usually attributed to psychosocial distress, depression, and polypharmacy.
- The weakness of the abdominal and pelvic muscles, limitation in physical activity, the self-restraint of fluids and a diet low in fiber can cause constipation, which indirectly may impair intake of food.
- Despite the reduction in lean body mass, ALS patients can have some increased energy requirements due to increased work of breathing, lung infections and other factors not yet well established.
- Cognitive dysfunction (20–50% of cases), mainly frontotemporal dementia.

ALS presents in two main different forms: bulbar progressive paresis (bulbar onset, 25–35% of patients) or spinal motor neuron injury (limb onset or peripheral onset). Almost 80% of ALS patients with bulbar onset will develop dysarthria and dysphagia. In a spinal or peripheral onset of the disease muscle weakness is the main symptom. Patients with bulbar onset and older age have the shortest life expectancy. Mean survival of ALS is 3–5 years, with 5%–10% living longer than 10 years [26]. Eventual respiratory failure and malnutrition with dehydration are the primary cause of death.

3.1. Clinical Question 1: Is nutritional status a prognostic factor for survival in ALS patients?

Recommendation 1:

At diagnosis, a complete nutritional assessment is recommended in ALS patients, including Body Mass Index (BMI),
weight loss over time and lipid status. Body composition analysis using DEXA or BIA with validated formula should be performed if available.

**Grade of recommendation:** B – strong consensus (100% agreement)

**Recommendation 2:**

During the follow-up, nutritional status assessment (BMI, weight loss) is recommended over time, in order to detect early malnutrition and plan for treatment. Body composition analysis should be performed if available.

**Grade of recommendation:** B – strong consensus (100% agreement)

**Commentary:**

The effect of nutritional status on the prognosis of patients with ALS depends on which parameter is being evaluated and the time when it is evaluated.

At diagnosis: With regard to the BMI and loss of BMI, BMI baseline was associated with survival (Hazard Ratio [HR] = 0.94 [95% CI: 0.90–0.98]; p = 0.005). (HR = 0.95 [95% CI: 0.91–0.99]; p = 0.01) [26,27]. For a loss of 1 BMI point the risk of death was of 9–23% higher (HR = 1.09 [95% CI: 1.03–1.15]; p = 0.004) [HR = 1.23 [95% CI: 1.07–1.41]; p = 0.003] [28,29].

Regarding the initial weight loss, patients losing more than 5% of their weight compared to usual weight had 2 times risk of death (HR = 1.92 [95% confidence interval [CI]: 1.15–3.18]; p = 0.01) [28]. Moreover after adjusting for known prognostic factors (age, gender, form of bulbar onset, diagnosis delay, amyotrophic lateral sclerosis functional rating scale [ALSFRS], manual muscular testing, forced vital capacity [FVC]) for a weight loss of 5% at diagnosis compared to usual weight the risk of death was increased by 14–30% (HR = 1.14 [95% CI: 1.05–1.23 ]; p = 0.002), (HR = 1.30 [95% CI: 1.08–1.56]; p = 0.006) [28,29]. In addition, weight loss of 10% at diagnosis entailed an increase in the risk of death of 45% (HR = 1.45 [95% CI: 1.06–1.99]; p = 0.046) [29].

Malnutrition at diagnosis was not associated with survival [28,29].

Focusing on bioelectric impedance phase angle (PA) and body composition, initial higher PA reduced the risk of death of 20% (HR = 0.80 [95% CI: 0.65–0.98]; p = 0.003) [27]. An increased risk of death of 29% was found for a loss of 1 degree of PA (HR = 1.29 [95% CI: 1.02–1.63]; p = 0.003) [28]. There was no association between survival and body composition (fat-free mass [FFM]) [26,28].

Hypermetabolism (resting energy expenditure [REE] measured – REE calculated)/REE calculated > 10%), was not association with survival [30].

A decrease of serum albumin was a risk of death factor (men: HR = 1.39 [95% CI: 1.05–1.90]; p = 0.02 and women: HR = 1.73 [95% CI: 1.35–2.39]; p = 0.001) [31].

Looking at serum lipids, a decreased LDL/HDL-cholesterol ratio increased the risk of death by 35% (HR = 1.35 [95% CI: 1.08–1.69]; p = 0.007) [32]. Inversely, a higher LDL/HDL-cholesterol ratio decreased the risk of death by 17% (HR = 0.83 [95% CI: 0.71–0.92]; p = 0.027) [31,33]. In addition, a high levels of total cholesterol, LDL-cholesterol and triglycerides at diagnosis were associated with better survival [27,31,33,34].

During the follow-up: Malnutrition, was an independent prognostic factor for survival with a risk of death increased by 2.2–7.4 fold in case of malnutrition (95% CI: 1.09–4.25; p = 0.01), (95% CI: 1.7–32.1; p < 0.01) respectively, (after adjusting for ALS-form, disease duration prior to consultation, duration of niluzole treatment, age at onset, and presence of a gastrostomy) [28,35]. On U-shaped curve a higher percentage of death was found in case of malnutrition and class III obesity [36].

Regarding the weight loss, a weight loss over 20% after the gastrostomy was associated with an increased risk of death (HR = 1.04 [95% CI: 1.02–1.06]; p = 0.01) [37]. In addition, each weight loss of 5% was associated with an increased risk of death of 34% (HR = 1.34 [95% CI: 1.18–1.51]; p < 0.0001) [28].

With regard to the variation of BMI, each loss of 1 point of BMI was associated with increased risk of death of 24% (HR = 1.24 [95% CI: 1.13–1.36]; p < 0.0001) [28]. A loss of more than 2.5 points of BMI had a shorter survival with 2.7 times risk of death (HR = 2.74 [95% CI: 1.47–5.13]; p = 0.001) [38,39]. Inversely, every gain of 1 point of BMI the risk of death was reduced by 14% (HR = 0.86 [95% CI: 0.80–0.93]; p = 0.0001) (after adjustment for age, cardiovascular disease, beginning of symptoms and FVC) [36].

Regarding the PA and body composition, an increase of risk of death for each loss of 1 degree of PA (HR = 1.88 [95% CI: 1.27–2.23]; p = 0.0003) [28], PA and FFM decrease were associated with shorter survival, regardless of weight loss [39]. In addition, patients with higher fat mass (FM) during the disease had a significantly increased survival, for an increase of 2.5 kg of FM the risk of death was reduced by 10% (HR = 0.90 [95% CI: 0.83–0.98]; p = 0.003) [28]. Bioelectrical impedance (BIA) with validated formula compared to dual-energy X ray absorptometry (DEXA) is a simple, fast and available method to assess body composition of ALS patients in clinical practice [40]. Although the gold standard to assess the body composition is DEXA, this method is more expensive, less available and rarely used on ALS [41].

In summary, nutritional status (malnutrition, BMI, weight loss, BMI loss, body composition, and lipid status) is a prognostic factor for survival in Motor Neuron Disease-ALS patients. At diagnosis, weight loss, BMI, PA and lipids status are prognostic factors for survival. During the follow up, malnutrition, weight loss, BMI loss and body composition are prognostic factors for survival. Nutritional risk assessment should be encouraged, using a validated malnutrition screening tool. See supplementary data for Clinical Question 1.

**3.2. Clinical Question 2: What are nutritional requirements in ALS patients?**

**Recommendation 3:**

Energy requirements in non-ventilated ALS patients should be estimated if indirect calorimetry is not available. Calculations should be estimated as approx. 30 kcal/kg body weight depending on physical activity, and adapted to weight and body composition evolution.

**Degree of recommendation:** GPP – strong consensus (100% agreement)

**Commentary:**

Determination of nutritional requirements in ALS patients requires estimation of their total energy expenditure (TEE), which consists of the sum of the energy expenditure related to resting energy expenditure (REE), food-related thermogenesis and physical activity. The gold standard to measure REE is indirect calorimetry. However, it is generally not available in clinics, leading to the use of equations to estimate REE. Mean predicted energy expenditure generally corresponds to measured REE at a population level [42]. However, a study including 34 ALS patients showed that REE estimated by the Harris–Benedict equation is not valid compared to indirect calorimetry because of limits of agreement ranging from –677 to +591 kcal/day, leading to under- or overfeeding in the majority of patients [43]. The limited validity of equations to
estimate REE in individual ALS patients has been later confirmed [44,45]. Kasarkis et al. also found a large variation of TEE measured by doubly-labeled water in 80 ALS patients and reported that TEE corresponds to REE in some patients but greatly exceeds REE in others [44]. This suggests not only that REE is variable but also energy expenditure related to physical activity.

Thus, as energy expenditure in ALS patients cannot be properly calculated in clinical routine, nutritional requirements have not been clearly determined. Some authors suggest relying on fat-free mass–adjusted REE, estimated around 34 kcal/kg body weight in ALS patients breathing spontaneously [42]. Other suggest to use the Harris–Benedict equation adjusted for correction factors to evaluate nutritional requirements and then to adapt the intakes according to evolution of weight and body composition [46,47].

There is insufficient data to perform any recommendations about protein requirements for ALS patients, and common determining factors should be considered: age, kidney function, degree of stress.

**Recommendation 4:**

Non-invasive ventilation is generally associated with a lower REE than spontaneous breathing or predicted by the Harris–Benedict equation. In the absence of indirect calorimetry, energy requirements should be estimated as 25 – 30 kcal/kg body weight or using the Harris–Benedict equation, and adapted following the evolution of body weight and the clinical situation.

**Degree of recommendation:** 0 — strong consensus (95% agreement)

**Commentary:**

A recent study shows that non-invasive ventilation reduces REE by 7% in 16 ALS patients compared to spontaneous breathing, due to decreased activity of inspiratory neck muscle [48]. Siirala et al. showed that measured REE was 33.6% lower in five ALS patients under intermittent positive pressure ventilation, than the mean REE estimated by 5 different predictive equations [49]. Shimizu et al. also found a reduced measured REE in 11 mechanically ventilated patients compared to REE estimated by the Harris–Benedict equation [50]. In contrast with these studies, Sherman et al. showed a higher measured REE than predicted by the Harris–Benedict equation in 18 ALS patients under mechanical ventilation. They hypothesized that these results were due to higher cytokine secretion, more fasciculations or refeeding, as many of these patients had been hospitalized for Percutaneous Endoscopic Gastrostomy (PEG) placement [43]. Ichihara et al. measured TEE by doubly-labeled water in 10 bedridden Japanese ALS patients who were under 24 h tracheostomy positive pressure ventilation [51]. They reported that the ratio of TEE over fat-free mass derived from total body water measurement was 35 ± 5.5 kcal/kg/day, thus similar to the value found in non-ventilated patients. In 3 patients, they measured REE by indirect calorimetry and showed that the ratio of TEE over REE was 1.05, thus that energy expenditure related to physical activity was negligible. See supplementary data for Clinical Question 2.

**3.3. Clinical Question 3: Should ALS patients gain weight or not?**

**Recommendation 5:**

In ALS patients, weight loss is detrimental for survival, but whether oral or EN should aim at weight stabilization or weight gain has not been clarified and may depend on baseline nutritional state. Weight gain should be recommended in patients with a baseline body mass index (BMI) < 25.0 kg/m², weight stabilization in those with a BMI between 25 and 35 kg/m², and weight loss in patients with a BMI > 35 kg/m² in order to improve passive and active mobilization.

**Degree of recommendation:** GPP — strong consensus (95% agreement)

**Commentary:**

Several studies have shown that a weight loss > 5 – 10% habitual weight or a BMI below 18.5 kg/m² at the time of diagnosis has been associated with decreased survival [35,39,52]. Furthermore, weight loss > 10% at the time of PEG placement was also associated with an increased mortality in multivariate analysis (RR 4.18, 95% CI 2.72–6.42) [53]. This raises the question whether increasing body weight is beneficial once ALS has been diagnosed [54].

Nutrition therapy (oral nutrition supplementation and enteral nutrition) may stabilize body weight in ALS patients [55,56], but no studies have evaluated whether this intervention is associated with an improved survival. Based on several studies, the American Academy of Neurology states that EN by PEG may improve survival in ALS patients [55]. In contrast, the guidelines of the European Federation of Neurological Societies report no convincing evidence for an improved survival with EN by PEG [57]. See supplementary data for Clinical Question 3.

**3.4. Clinical Question 4: What is the prevalence and natural history of oropharyngeal dysphagia in ALS?**

**Specific prevalence of nutritional and respiratory complications in patients with ALS:**

- **Malnutrition and aspiration pneumonia**

**Recommendation 6:**

Due to the high prevalence and the impact on nutritional status and risk for respiratory complications, dysphagia screening is recommended in every ALS patient.

**Grade of recommendation:** B — strong consensus (100% agreement)

**Recommendation 7:**

Screening for malnutrition (BMI, weight loss) is recommended at diagnosis and during the follow-up every 3 months.

**Grade of recommendation:** B — strong consensus (95% agreement)

**Commentary:**

**Natural history of oropharyngeal dysphagia:**

Oropharyngeal dysphagia is a severe and invalidating symptom for ALS patients [58]. Swallowing disorders disturb the ability to move food or liquids safely and efficiently from the mouth through the pharynx into the esophagus. The weakness of muscles involved in the oral and preparatory phase of deglutition leads to a poor lip seal with drooling and trap food particles in the buccal sulcus [12,59]. Weakness of masticatory muscles leads to a poor chewing and impairs the ability to form a normal food bolus, and weakness of tongue muscles impairs the tongue ability to propel the food bolus. During the pharyngeal phase, a reduction of the soft-palate closure leads to reflux of food and liquid into the nose. At last, alteration of pharyngeal peristalsis leads to a high risk of aspiration during swallowing due to incomplete epiglottic closure. Dysphagia is more often found in patients with bulbar onset but patients with spinal onset can also develop swallowing disorders [58]. Nearly all patients with ALS manifest bulbar involvement in advanced disease. Swallowing disorders affect food intake, with an increase of meal time and asthenia during and after the meal [12]. During ALS,
swallowing changes may occur in 5 stages: 1) normal eating habits; 2) early eating problems such as difficulty of chewing; 3) dietary consistency changes; 4) a need for tube feeding and 5) nothing by mouth [59,60]. Consequently, these disorders will cause an alteration of nutritional status with weight loss and a risk to develop a state of malnutrition. At short, medium or long term, worsening swallowing disorders and nutritional status put the indication of artificial nutrition by feeding tubes, gastrostomy is preferable [57]. Dysphagia can lead not only to aspiration pneumonia and malnutrition, but can also alter quality of life, with anxiety during the meal for patients and their caregivers [57,58,61].

Prevalence of dysphagia: The prevalence of dysphagia is variable in different studies depending on the evaluation method (patient interview, bedside examinations, swallowing scale, videofluoroscopic evaluation, endoscopic evaluation), the time of disease progression and the predominant type (spinal/bulbar) of the evaluated patients. With endoscopic evaluation, 47.8%–72.7% of dysphagia was found mainly in patients with bulbar form [38,62,63]. With videofluoroscopic evaluation of swallowing, 75% of patients had dysphagia [64]. Closed to 48% of dysphagia were found (through bedside examinations and the Dysphagia Limits amounts of 20 ml or more at a time) [65,66]. With clinical assessment, 6% of isolated dysphagia and 15% of dysphagia and dysarthria were found (35% of bulbar form) [67]. The prevalence of dysphagia after patient interview was found in 85.7% of cases in bulbar form, 42.9% in upper limbs form and in 71.4% in lower limbs form [33,4%] [68]. With a same assessment 34.7% of dysphagia was found (21.4% of bulbar form) [69]. Using a swallowing scale 41.1% to 70.0% of swallowing disorders were found [66,70]. Dysphagia as an initial symptom of ALS was found in 6.2% of patients [69].

Prevalence of malnutrition: At diagnosis, with BMI criteria (<18.5 kg/m²) malnutrition was found in 0%–11.1%, 10.1% (<20 kg/m²) and 8.7%–13.0% (<18.5 kg/m² if age <70 years and <21 kg/m² if age >70 years) [26,28–30,38,72]. With weight loss criteria (>10%) malnutrition was found in 21.0% [29,70]. During the follow-up, with BMI criteria (<18.5 kg/m²) 2.1%–20.1%, (<20 kg/m²) 16.1%–26.4% and (<18.5 kg/m² if age <70 years and <21 kg/m² if age >70 years) 7.5%–15.2% of patients were malnourished [28,35–37,44,64,72,77]. With weight loss criteria (weight loss >10%) 25.0% to 48% and 24.5% (weight loss >20%) of malnutrition was found [72–74]. At the time of gastrostomy 17.8% (<18.5 kg/m²) and 27.4%–53.0% (<20 kg/m²) of patients were malnourished [75,76].

Prevalence of aspiration pneumonia: 13% of aspiration pneumonia was found [73]. In a post mortem study of the cause of death, aspiration pneumonia was found in 11.4% of cases [74]. However, in this study, 41% of patients died because of a bronchopneumonia, and another 9% of patients due to respiratory failure. In summary, dysphagia is found in 6.2–85.7% of ALS patients (48.1–85.7% in bulbar form and 41.1–71.4% in spinal form). At diagnosis, malnutrition is present in 0–21% depending on the criteria used to evaluate and in 7.5–53% during the follow up. Few studies assessed the prevalence of aspiration pneumonia, and this prevalence is close to 15%. Considering the median survival of 18–28 months and the risk of impaired nutritional status with dysphagia, follow up every 3 months is recommended [28,29,66]. See supplementary data for Clinical Question 4.

3.5. Clinical Question 5: At what stage of the disease do we need to screen for dysphagia in ALS patients?

Recommendation 8:

We recommend that screening for dysphagia should be performed in all ALS patients, both at diagnosis and during follow up, as part of a comprehensive clinical and neurological evaluation. The frequency of dysphagia clinical evaluation at follow-up should depend on the presence and the progression of clinical signs. In general, a 3 months frequency can be recommended.

Grade of recommendation: GPP – strong consensus (91% agreement)

Commentary:

Several studies revealed some alterations in the swallowing capacity in ALS patients at an early stage of the disease, even in the absence of bulbar symptoms. Thus, both symptoms and clinical signs of dysphagia should be evaluated, as part of a comprehensive clinical and neurological evaluation, in every ALS patient, at the time of diagnosis and during the following clinical evaluations. The frequency of dysphagia clinical evaluation at follow-up should depend on the presence and the progression of clinical signs. In general, a 3 months frequency evaluation can be recommended [55].

Clinical severity scales of ALS such as “ALS functional rating scale-revised” (ALSFRS-R) or ALS Swallowing Severity Scale (ALSSS) include data regarding the presence or absence and the severity of dysphagia [75]. These scales are usually based on patient’s symptoms. A new scale for dysphagia in patients with progressive neuromuscular diseases, including motor neuron disease (MND), has recently been developed [76].

Clinical assessment of dysphagia should include evaluation of lip closure and evidence of saliva pooling, tongue strength, mobility and tone, chewing capacity, palatal movement in response to tactile stimulation, the quality and strength of the cough as well as phoniatric function. Facial and lateral jaw movements are usually normal in the early stages of ALS [12]. A swallow test can also be performed [77]. Volume-Viscosity Swallowing Test (V-VST) has been shown to have a high sensitivity to identify patients at risk of aspiration. Instrumental assessment of dysphagia, videofluoroscopy (VFS) or fiberoptic endoscopic evaluation of swallowing (FEES) is usually performed according to local protocols, in patients with symptoms of dysphagia. There are no studies comparing different protocols in ALS patients. See supplementary data for Clinical Question 5.

3.6. Clinical Question 6: Are there specific methods for screening and clinical diagnosis of oropharyngeal dysphagia in ALS?

Recommendation 9:

There are no specific methods available to screen or clinically evaluate dysphagia in ALS patients, and general screening and evaluation methods for neurological disorders are appropriate. Structured questionnaires, water swallow tests and volume-viscosity swallow test can be applied. Instrumental techniques (videofluoroscopy, videofluoromamomery and flexible endoscopic evaluation of swallowing) allow detecting early signs of dysphagia in ALS patients.

Grade of recommendation: B – strong consensus (96% agreement)

Commentary:

There are no clinical studies on any specific method for screening and clinical diagnosis of OD in ALS patients. Structured questionnaires for screening of OD, such as EAT-10, have been tested in ALS patients. One study has evaluated the discriminatory ability of EAT-10 to identify patients with unsafe airway protection during swallowing. Seventy ALS patients, with a mean disease duration of the disease of 17.9 months (range 2–72, DS 13), ALSFRS-R score of 34.8 (range 16–47, DS 7.9) completed an EAT-10 questionnaires and underwent a videofluoroscopic evaluation of
swallowing. In this study, EAT-10 offered high discriminant ability to identify ALS patients who aspirate (sensitivity 86%, specificity 76% negative predictive value 95%) [78]. Water swallow tests and the V-VST [79] has also been used for clinical screening and evaluation of OD in ALS patients. Twenty patients were evaluated in one study. In comparison with videofluoroscopy, the sensitivity of V-VST to detect OD in ALD patients was 92%, and specificity 80% (p = 0.007). The evaluation of voluntary cough airflow can also differentiate safe and unsafe swallowing in ALS patients [80].

Videofluoroscopy is considered one of the main diagnostic tools for the clinical evaluation of OD in ALS patients [55]. The protocol includes the use of different consistencies and volumes of contrast bolus. VFS can contribute to examine the different phases of the swallowing process as well as the presence of oral or pharyngeal residue. It can identify silent aspirations and can evaluate the effect of compensatory postures in ALS patients with dysphagia [81]. Several cross-sectional and cohort studies have been published that assessed the role of VFS in identifying swallowing abnormalities in ALS patients [82–86]. VFS can also be performed in conjunction with pharyngeal manometry and can show alterations even in ALS patients with normal VFS [87,88]. Manometry in ALS patients have revealed low tongue driving forces and pharyngeal contraction amplitudes and normal relaxation of the upper esophageal sphincter [89]. Data have shown a decrease of the pharyngeal force with the progression of the disease [90].

Fiberoptic endoscopic evaluation of swallowing (FEES) is a bedside clinical evaluation that can be considered an efficient method in the assessment of OD [78]. FEES can identify impaired chewing, tongue muscle deficit, velo-pharyngeal closure competence, laryngeal morphology and motility, and cough reflex sensitivity and to detect eventual pharyngeal residues [91]. FEES effectiveness has been evaluated in ALS patients. In a cross-sectional historical cohort study including 11 patients, of which 72.7% complained of dysphagia, oral or pharyngeal alterations were observed in all studied individuals [92]. In a longitudinal study in 49 ALS patients, the presence of chewing deficit could predict dysphagia at 12 months follow-up [62].

Ultrasonography can also be used in the clinical evaluation of OD in ALS patients, as it can identify tongue thickness alterations [58], and has a high sensitivity to identify early alterations in the oral phase of the swallowing process, such as abnormal bolus position or reduced or disorganized lingual movement [93].

Oropharyngeal scintigraphy permits a functional and semi quantitative evaluation of the various stages of swallowing and has been used in ALS patients [94].

In summary, there are no specific methods for the screening and clinical diagnosis in ALS patients. Both EAT-10 and volume-viscosity swallow test have been shown to have high sensitivity and specificity in the identification of patients with unsafe swallow. Videofluoroscopy, videofluorometric and FEES can detect early signs of dysphagia in ALS patients. Other methods, such as ultrasound or scintigraphy have been also employed in ALS patients. Most studies included a limited number of patients, with different clinical characteristics and time from diagnosis. More studies are needed to further evaluate the clinical efficacy of these techniques in ALS patients. See supplementary material for Clinical Question 6.

3.7. Clinical Question 7: What are the specific and frequent videofluoroscopic (VFS) signs in patients with ALS?

**Recommendation 10:**

Videofluoroscopy study can detect early signs of dysphagia in ALS patients, and should be recommended in the clinical evaluation of dysphagia in these patients at diagnosis of the disease.

**Grade of recommendation: GPP — strong consensus (95% agreement)**

**Commentary:**

Videofluoroscopy can evaluate the physiopathological alterations in the swallowing process and detect silent aspirations in patients with OD. A penetration/aspiration scale has been proposed [95].

Several studies have evaluated these alterations in ALS patients. Initial studies described that the oral phase of swallowing was the most compromised, followed by the pharyngeal phase [82]. One study evaluated 23 ALS patients with clinical dysphagia, according to ALS Severity Score (ALSSS) [83]; A clinical evaluation of OD was performed using VFS, FEES and manometry. The most prevalent VFS findings in these patients were oral stasis of residual barium (9/13), piecemeal swallowing (6/13), incomplete relaxation of upper esophageal sphincter and decreased pharyngo-esophageal motility. Aspiration was observed in 6/13 patients. Other studies have also observed an early alteration in oral phase of the swallowing process in ALS patients with mild dysphagia [87]. In a study performed in 23 ALS patients, swallowing alterations were present in 66.7% of patients with “normal eating habits” on the ALSSS scale, 33% in the oral phase and 75% in the pharyngeal phase (especially pharyngeal contraction reduction) [84]. In five patients (41.6%), bolus stasis in the pharynx was observed and induced episodes of post-swallowing penetration.

In a longitudinal study in 72 examinations in 50 ALS patients, delayed bolus transport from the oral cavity to the pharynx, and bolus stasis in the pyriform sinus were seen in about half of the patients with no bulbar symptoms [84]. Upper esophageal sphincter opening was preserved in 2/3 of patients with more than 24 months of disease progression. Bolus holding in the oral cavity, constriction of the pharynx and elevation of the larynx worsened progressively over time. The frequency of aspiration also increased over time.

One recent study has evaluated the VFS signs of dysphagia at the initial diagnosis of ALS in 19 patients [86]. Six patients presented only bulbar disorder and 8 presented a combination of bulbar and extrtemity symptoms. Fourteen physiological components of swallowing and the presence or absence of oral and pharyngeal residue were evaluated. Regarding oral phase, lip closure, lingual elevation and tongue movement to palatal seal were preserved in both bulbar symptoms-negative and bulbar symptoms-positive patients. Both components of bolus preparation/mastication, and initiation of pharyngeal swallow were preserved in bulbar symptoms-negative patients, but impaired in bulbar symptoms-positive patients. The components of bolus transport and oral residue were affected regardless the presence of bulbar symptoms. In the pharyngeal phase of swallowing, it was shown that soft palate elevation and retraction, laryngeal elevation, anterior hyoid excursion, laryngeal closure, pharyngo-oesophageal segment opening, tongue base retraction and epiglottic inversion were preserved in bulbar symptoms-negative patients. When the patients presented bulbar symptoms, laryngeal elevation, anterior hyoid excursion and tongue base retraction were impaired. Pharyngeal residue was affected in all patients.

Videofluorometric studies (VFM) have observed that the decrease in the swallowing pressure first appears in the oropharynx [90]. In 40 ALS patients with dysphagia videofluoroscopic dysfunctions of the oral phase of swallowing, pharyngeal initiation, pharyngeal transport and manometric data revealed low tongue driving forces and pharyngeal contraction amplitudes but normal relaxation of the upper esophageal sphincter [89]. Other VFM study in 10 ALS patients with no symptoms of dysphagia and a normal VFS observed an increase in the pharyngeal contraction time and in residual pressure after relaxation of the upper esophageal sphincter [89].
In summary, frequent VFS signs in patients with ALS are delayed bolus transport from oral cavity to pharynx and decreased pharynx contraction. Videofluoroscopy can reveal alteration in the swallowing process in asymptomatic ALS patients. See supplementary material for Clinical Question 7.

3.8. Clinical Question 8: What are the therapeutic effects of behavioral, rheological and rehabilitation treatments for OD in patients with ALS?

**Recommendation 11:**

In ALS patients with muscular fatigue and long lasting meals, patients should be advised to fractionate and enrich their meals with energy or deficient nutrients. If weight loss progresses, oral nutritional supplementation should be recommended.

*Grade of recommendation: GPP — strong consensus (95% agreement)*

**Recommendation 12:**

In ALS patients with moderate dysphagia, dietetic counseling should be advised to adapt the texture of solid and liquids to facilitate swallowing and avoid aspiration. Instrumental study of swallowing function (VFS, FEES or VFS-manometry), if available, can guide the security and efficacy of the texture-modified diet.

*Grade of recommendation: GPP — strong consensus (100% agreement)*

**Recommendation 13:**

In ALS patients with moderate dysphagia, postural maneuvers (such as chin-tuck posture) should be recommended to protect the airway during swallowing.

*Grade of recommendation: GPP — strong consensus (100% agreement)*

**Commentary:**

There is no strong evidence in the literature for dysphagia intervention (compensatory and rehabilitative practices) in patients with ALS, probably due to the difficulty in the design of RCT in this devastating disease. Furthermore, some compensation techniques described in the literature for the treatment of dysphagia cannot be directly used in ALS patients due to the physiopathology of dysphagia and the special relevance on muscle atrophy and fatigue.

Patients who experience appreciable levels of fatigue should be advised to eat their food as several small meals a day. Dietetic counseling should focus on meal enrichment by use of high-calorie foods. In case of constipation caused by abdominal weakness, dietary fiber can be added to the diet. The triggering of the swallowing reflex can be enhanced by emphasizing taste or temperature.

**Adapting bolus characteristics:** The initial management of dysphagia is based on dietary counseling, and modification of food texture (soft, semisolid or semiliquid states) is often required to compensate for a poor oral preparation phase and ease oral and pharyngeal transport while avoiding episodes of choking [57,96,97]. In patients whose swallowing is delayed, the use of thicker liquids, semisolid foods with a high water content, such as jellified water are suggested as better alternatives to thinner liquids and can help alleviate aspiration. However, there is not sufficient evidence in the literature to assess the efficacy of the modified-consistency food and liquids in the treatment of dysphagia in ALS patients.

**Postural maneuver:** Solazzo [81] assessed the effect of different postural maneuvers in 81 ALS patients with dysphagia evaluated with videofluoromanometry: chin-down, or chin-tuck posture, head-rotation posture and hyperextended head posture. The results of the study showed that swallowing disorders in patients with ALS differ according to the mechanism involved in relation to disease features and progression. Of the three postural maneuvers, the chin-tuck posture proved to be useful in the majority of cases, given that it offers a valuable protection mechanism for the airways by opening the valleculae and preventing penetration into the larynx. Head rotation is indicated in the case of hypertonicity, incomplete release or premature UES closure, and hyperextended head posture is indicated in the absence of lingual pump only if safe transit is ensured. Lastly, in the frequent case of penetration without aspiration into the laryngeal inlet (23% of patients), throat clearing every three to four swallowing acts can prevent possible postswallowing inhalation. Gooleven [89] evaluated 40 patients with VFM, and found that both the oral as well as the pharyngeal stage of swallowing may be compromised in the majority of ALS patients (97%), and aspiration, even without clinical aspiration signs or subjective complaints, can be present in 22% of patients. No specific postural maneuvers were suggested in this article.

**Other therapies:** Saliva problems have been studied with respect to their possible relation with dysphagia management. Both volume and saliva have been proposed as factors that can negatively affect swallowing in ALS patients. Recently, the National Institute for Health and Care Excellence (NICE) [98] has addressed the saliva problems for nutrition management in people with motor neuron disease (MND) and found only indirect evidence from other study populations to recommend pharmacological treatments as antimuscarinic therapy or botulinum toxin A to manage sialorrhoea. No evidence has been found to link the treatment of saliva problems with the improvement of dysphagia. See supplementary data for Clinical Question 8.

3.9. Clinical Question 9: Do early oral protein-energy supplements improve survival in ALS patients?

**Recommendation 14:**

Nutritional supplementation is recommended for ALS patients who do not cover their nutritional requirements with an enriched diet. However, there is insufficient data to affirm that oral nutritional supplementation can improve survival in ALS patients.

*Grade of recommendation: GPP — strong consensus (100% agreement)*

**Commentary:**

Few interventional studies with control group exist and focused on this subject. The study of Dorst et al. in 2013 compared the impact of two oral nutritional supplements (ONS) high caloric/high fat versus high caloric/high carbohydrate taken during the disease (3 x 200 ml, 150 kcal per 100 ml. ONS with high fat contained 35% fat, 50% carbohydrate, and 15% protein, high carbohydrate contained ONS with 0% fat, 89% carbohydrate, and 11% protein) [56]. No survival analysis was performed during this study. A caloric supplementation with carbohydrates seems beneficial on survival. Indeed, a recent study of Wills et al. in 2014 found better survival in patients taking this supplementation (1.5 kcal/ml of which 29.4% calories are from fat) administered with feeding tube during the disease compared to controls having an isocaloric diet during 5 months of follow-up (p = 0.01) [59]. There was no significant difference between the control group and patients taking high caloric/high fat supplementation (1.5 kcal/ml of which 55% calories are from fat). Two interventional double blind studies with control group are in the process of inclusion of patients. The first carried out in France,
consists to give at diagnosis 1, 2 or 3 high caloric/high protein oral nutritional supplements (300 kcal/unit and 18 g of protein/unit or 322 kcal/unit and 18.6 g of protein/unit) versus group control. The second carried out in Germany consists to give high caloric/high fat ONS (4.5 kcal/ml, 100% lipids) 405 kcal/90 ml/day versus placebo 8 kcal/90 ml/day [100] In summary, there are few data available in the literature to clearly answer this question. Some ongoing studies can help to answer in a most appropriate form this clinical question. See supplementary data for Clinical Question 9.

3.11. Clinical Question 11: Does EN improve survival in ALS patients?

Recommendation 16:

Survival benefits of EN in ALS patients depend on disease presentation and rate of disease progression. We recommend to consider EN in all ALS patients in whom nutritional needs cannot be met by oral feeding and in whom it is estimated that malnutrition/dehydration could be responsible of reduced survival.

Grade of recommendations: B – strong consensus (100% agreement)

Commentary:

Nutrition is of great concern in ALS as weight loss, malnutrition and dehydration may aggravate muscle weakness, contribute to respiratory weakness, and affect survival [102]. Weight loss is a sign of poor prognosis, and the maintenance of a patient’s weight may prolong survival. It has to be highlighted that ALS are diseases which change rapidly and as such it is important to assess hydration, feeding ability, swallowing and nutritional factors, including intake, at every possible opportunity to prevent weight loss [98]. Morassutti et al. documented that if ALS patients are treated before any significant weight loss occurs, the early nutritional intervention allows good nutritional status to be maintained for a longer period and reduces mortality rate [103]. With inevitable disease progression, dysphagia and swallowing complications significantly contribute to reduced survival [104].

The importance of nutritional management is being increasingly recognized but the evidence for a survival advantage after EN is conflicting [26]. Recently, Chhetri et al. did not find a survival advantage with EN except for those patients who received it more than 500 days after symptoms onset, suggesting that the early requirement for EN may indicate an aggressive illness and therefore a less favorable prognosis [105]. A Cochrane systematic review [102] showed the results of 11 controlled studies comparing PEG feeding to oral feeding. All of these 11 studies tested for a possible survival advantage. Moreover, in patients who underwent PEG placement early in their disease course, survival increased likely owing to the improvement of their nutritional status [106,107]. The lack of a survival advantage should however not dissuade clinicians from recommending enteral feeding to patients with dysphagia and/or malnutrition. See supplementary data for Clinical Question 11.

3.12. Clinical Question 12: What is the best timing for gastrostomy tube in ALS patients? Is there a relationship between survival and respiratory function at the time of gastrostomy?

Recommendation 17:

Gastrostomy should be discussed at an early stage, and at regular intervals as ALS progresses, according to the evolution of the swallowing problems of safety and efficacy. The detection of dysphagia, long duration of meals, weight loss, poor respiratory function, risk of choking and wishes of the patients should guide the decision to place the gastrostomy.

We recommend to perform the gastrostomy before severe weight loss occurs and before respiratory function is severely impaired.

Degree of recommendation: GPP- strong consensus (100% agreement)

Recommendation 18:

The decision to place a gastrostomy should be made in collaboration with the patient following discussion of his/her wishes and the risks and benefits of the procedure.

Degree of recommendation: GPP – strong consensus (100% agreement)
Recommendation 19:

The benefits of early placement of a gastrostomy should be explained, as well as the possible risks of a late gastrostomy (low critical body mass, respiratory complications, different methods of insertion, and a higher risk of mortality and procedural complications due to low weight).

Degree of recommendation: GPP — strong consensus (95% agreement)

Commentary:

Gastrostomy feeding is recommended to provide long-term enteral nutrition therapy for patients with ALS with severe dysphagia [55]. However, current practice in relation to timing of gastrostomy insertion is not clear and is based on consensus and expert opinion. Recently, the NICE [98] has addressed the question about the appropriate timing of placement of a gastrostomy tube for nutrition management in people with MND. No RCT or relevant high quality studies were identified to answer this question, and they stated several recommendations based on informal expert consensus. Gastrostomy could be beneficial for the survival, quality of life, and nutritional outcome of patients with ALS, but there is a lack of high-quality evidence relating to these aspects of the intervention because of ethical reasons to perform a randomized control trial. For this reason, the best evidence should be acquired through prospective cohort studies comparing patients undergoing gastrostomy with those who refuse the procedure, or from large retrospective studies focusing on patients underwent gastrostomy.

McDermott et al. [108], in a large, longitudinal, prospective study (ProGas) explored the 30-day mortality after gastrostomy placement in a multicenter study including 330 ALS non-ventilated patients, and as secondary outcomes they analyzed complications of the gastrostomy insertion procedure, median survival time from gastrostomy placement, nutritional status change and self-perceived quality of life changes after gastrostomy. In this study, the regression model to assess mortality risk included variables as weight loss at the time of gastrostomy compared with weight at diagnosis (<10% weight loss and >10% weight loss subgroups), forced vital capacity at the time of gastrostomy insertion, age at the onset of amyotrophic lateral sclerosis, site of amyotrophic lateral sclerosis symptom onset (bulbar and limb subgroups), and ALSFRS-R monthly decline rate. Prognostic factors for mortality at 30 days were significantly related with age of onset of ALS (HR 1.035 [95% CI 1.008–1.063]; p = 0.011) and weight loss before gastrostomy (>10% weight loss subgroup compared with the <10% weight loss subgroup, HR 2.514 [1.490–4.243]; p = 0.001). Gastrostomy feeding prevented weight loss in half of the patients, and led to weight gain in 25% of them. The nutritional data suggested that the greater the percentage of weight loss at the time of gastrostomy from diagnosis, the less likely the patients recovered this loss after gastrostomy. These results suggest that patients might benefit from early gastrostomy, i.e. before substantial weight loss that might not be reversible has occurred. Dorst et al. [109], in a multicenter trial, explored the outcome of 89 ALS patients submitted for PEG in a 3 years follow-up study. The overall survival from time of PEG insertion was 18.9 ± 1.6 months, independent of BMI, ALSFRS-r, and FVC. Patients with less overall weight loss (less than 5 kg) and higher cholesterol levels (>220 mg/dl) at time of PEG insertion had a better survival (21.5 ± 2.1 vs 15.3 ± 2.4 months, p = 0.025).

The relation between respiratory function and risk of mortality and outcome after gastrostomy has been a matter of controversial. Chió, in 2004 [110], alert about significant decreased survival in ALS patients with moderate to severe respiratory impairment underwent PEG, in comparison to those in which radiologically guided gastrostomy was performed. While the American Academy of Neurology [55] and ENFS Task Force [57] recommend to perform the gastrostomy with a forced vital capacity of >50% of predicted values, several studies demonstrate that gastrostomy could be performed with security in patients with worse respiratory function [111]. Pena [112] conducted a study with 151 ALS patients and analyzed the predictors for mortality after the gastrostomy placement. Of note, patients with FVC <50% at the time of gastrostomy were all on non-invasive ventilation and gastrostomy procedure was performed with ventilator support in patients with respiratory symptoms, low FVC or abnormal oximetry. Only age at diagnosis of ALS was identified as an independent prognostic factor for survival in this study, although patients with lower FVC (<50%) have higher first-month mortality. Spataro [113] analyzed the survival of 76 ALS patients with dysphagia that accepted PEG, and they compared the outcome with 74 ALS patients with dysphagia that refused the procedure. Among bulbar-onset patients, PEG users showed a median survival time longer than those with no PEG (28 months vs. 25 months), even though the difference was not significant. Conversely, spinal-onset patients with dysphagia and PEG lived significantly longer than those who refused PEG (44 months vs. 36 months, p = 0.046). Survival in patients with PEG was not affected by the severity of the respiratory impairment, as measured by forced vital capacity. In the study of Dorst [109], patients with a very compromised respiratory status were included (35 patients with FVC < 50% of predicted values), and survival was not different of patients with FVC > 50% (40 patients). There are no studies focusing on ALS patients with FVC below 30% of predicted values, but individual cases are included in some series [113]. The American Academy of Neurology [55] recommends to refuse gastrostomy when FVC was lower than 30%, and to consider other forms of palliative care. As a criticism for recommend or refuse gastrostomy depending on FVC, we should consider that ALS patients with dysphagia, in particular those with a primary bulbar involvement, may perform poorly on spirometry because weakness of the oro-facial muscles. See supplementary data for Clinical Question 12.

3.13. Clinical Question 13: What is the best approach for gastrostomy in ALS patients: percutaneous endoscopic gastrostomy or radiologic gastrostomy?

Recommendation 20:

We recommend PEG as the preferred approach for gastrostomy. When available, in more frail patients, RIG positioning by expert team may be indicated. PEG-J or PEJ may be considered in selected patients.

Grade of recommendation: 0 — strong consensus (97% agreement)

Commentary:

PEG is the most appropriate and commonly used enteral access for medium- and long-term EN. A viable alternative to PEG is represented by radiologically inserted gastrostomy (RIG). The greatest advantage of RIG is placement safety even in patients with significant respiratory impairment [114]. The disadvantages of RIG are the risk of obstruction, because of its small (narrow) diameter, and dislocation of the tube. Thornton et al. compared the effectiveness of RIG to PEG and, despite a greater technical success with RIG, they did not find differences in complications or survival rates between the two techniques [115].

The ProGas study documented that patients who underwent radiologically inserted gastrostomy had a significantly increased rate of gastrostomy tube-related complications because narrow in
diameter and not securely fixed as those inserted by PEG [108]. In contrast, Allen et al. performed a retrospective study on gastrostomy tube placement methodology and found that RIG was more often successful and less often associated with aspiration with respect to PEG [116]. The ProGas study indicates that overall mortality after gastrostomy insertion is independent of the gastrostomy method and is driven by the patient age at the onset of amyotrophic lateral sclerosis and the percentage of weight loss from diagnosis to the time point of gastrostomy [108].

Decision-making criteria that influence the selection of method of gastrostomy are: status of the respiratory function of the patient; clinical condition of the patient; anatomical issues contraindicating the use of a specific method; availability of service and patient management following gastrostomy [117]. Gastrostomy should be discussed at an early stage, as ALS-MND progresses, and it should take place without unnecessary delay. PEG remains the preferred method for gastrostomy for patients with good respiratory function (forced vital capacity >50%) and overall good clinical condition, whereas RIG is preferred, when available, for more frail patients with moderate or severe impairment of the respiratory function [117]. See supplementary data for Clinical Question 13.

3.14. Clinical Question 14: Is parenteral nutrition (PN) indicated in ALS?

Recommendation 21:

EN (tube feeding) should be preferred over PN in ALS patients who need nutritional therapy.

In the acute setting, PN can be used if EN is contraindicated or non-feasible.

Home PN is generally not indicated in ALS patients. In case of patient’ refusal or non-feasibility of EN, risk-to-benefit ratio, financial burden and ethical issues should be evaluated before considering Home PN.

Grade of recommendation: GPP – strong consensus (100% agreement)

Commentary:

Most reviews and clinical guidelines recommend the use of EN over PN in ALS patients who require medical nutrition therapy, as in other clinical situations [57,61,98]. In the acute setting and during a short-term period, PN can be indicated in ALS patients if EN is contraindicated or non-feasible (e.g. gastrointestinal hemorrhage, ileus, gastrostomy placement failure, etc.). Only a few studies have been published to assess the feasibility and complications of home PN in ALS patients. None of them have compared PN with other procedures (such as PEG or RIG) in a prospecitive way.

Verschuuren et al. undertook a single center study in 30 ALS patients with advanced ALS, who were treated with HPN because of respiratory insufficiency and EN was refused or impossible [118]. The results were compared with those obtained retrospectively on a group of 35 patients who underwent PEG, who were subdivided into patients with respiratory insufficiency (n = 9) and those without respiratory insufficiency (n = 26). PN was administered through a central venous catheter. Twenty patients received this treatment at home. Weight stabilization was achieved in most patients. Mean survival time was 3.5 ± 2.4 months. Twenty four patients died from respiratory failure, one patient from acute subdural hematoma. Death was due to a catheter related bloodstream infection in one patient and this cause was also suspected in another one. In patients with PEG and respiratory insufficiency, post-procedure survival was similar to that of patients on PN, and significantly lower than survival in patients without respiratory insufficiency. Quality of life of patients or caregivers was not specifically assessed in this study.

A French national survey has evaluated the safety of home PN in patients with ALS in a retrospective multicenter study [119]. Data from seventy-three patients, with a mean follow-up of 163 ± 197 days (11,908 catheter days) are described. Most patients were in advanced stage of their disease (mean disease duration 35 ± 37 months, mean FVC 39.6 ± 18%) Home PN was chosen because of severe respiratory failure (69%), gastrostomy refusal (22%), dementia (6%) or gastrostomy placement failure. The median survival after PN was 2.8 ± 1.12 months. Total central venous catheter complication rate was 3.11 per 1000 catheter days (1.93 septic and 1.09 mechanical complications). Death was due to septic shock in eight patients. Metabolic complications were frequent (2.62/1000 catheter days), but without serious consequences. See supplementary data for Clinical Question 14.

3.15. Clinical Question 15: Does physical activity improve survival in ALS patients?

Recommendation 22:

There is little evidence concerning the impact of physical activity once ALS has been diagnosed. Some evidence suggests that endurance as well as resistance exercises can slow the progression of the disease and may improve functionality as well as QoL. Thus, physical activity should be advised as long as it does not worsen the physical state of the patient.

Degree of recommendation: 0 – strong consensus (100% agreement)

Commentary:

A systematic literature review performed between 2002 and 2006 reported that physical activity is probably not a risk factor of developing ALS [120]. More recently, an observational study on 636 sporadic ALS patients and 2166 controls found a higher risk of ALS with higher leisure time physical activity (sports, hobbies). However, the authors could not find an association with the level of occupational physical activity nor a dose–response relationship between physical activity and ALS. They concluded that ALS may rather be promoted by a genetic profile or lifestyle mode related to physical fitness [121]. Another study included over 800’000 men born in Sweden, followed over 20 years. Eighty-five patients died from ALS. The authors found an association between cardiovascular fitness, measured or estimated, at baseline and death at an early age [122]. Thus, there are still conflicting results regarding the impact of physical activity prior to ALS diagnosis.

Few evidence exist concerning the impact of physical activity once ALS has been diagnosed. However, the studies published on that topic show that endurance as well as resistance exercises slow the progression of the disease and may improve quality of life [123]. See supplementary data for Clinical Question 15.

4. Parkinson’s disease

Parkinson’s disease (PD) is a chronic, progressive neurodegenerative disorder resulting from dopamine depletion in the brain. The main symptoms include tremor, muscular rigidity, bradykinesia and postural instability. As PD progresses, a variety of other symptoms emerge, including dysphagia, dysarthria impaired gastrointestinal motility and gastroparesis, fatigue, depression and cognitive impairment. Drug therapy is essential to control symptoms and to maintain mobility in PD, and acts by replacing or mimicking dopamine in the brain.
Patients with PD are at increased risk of malnutrition and weight loss, and nutritional status should be monitored routinely regularly throughout the natural history of the disease [124]. Malnutrition in PD patients is probably under-reported, and can be found in about 15% in community-dwelling patients with PD and other 24% patients are at medium or high risk of malnutrition [125]. Several predictors of malnutrition have been found: older age at diagnosis, higher levodopa equivalent daily dose/body weight, anxiety and depression and living alone.

Dysphagia in PD usually occurs in the advanced phases of the disease, although sometimes it is present at onset. Functional alterations in oropharyngeal and esophageal motility can be present in about 60–80% of patients, but must be asymptomatic. Gastro- intestinal dysmotility has potential implications for enteral feeding strategies.

4.1. Clinical Question 16: Do patients with Parkinson's disease (PD) have higher nutritional requirements?

**Recommendation 23:**

We recommend that PD patients should undergo regular monitoring of nutritional and vitamin status during the course of the disease. Particularly, attention should be focused on changes in body weight, and the need of supplementing vitamin D, folic acid and vitamin B12.

**Grade of recommendation B – strong consensus (91% agreement)**

**Commentary:**

PD patients experience several changes in body weight during the course of the disease [124,126,127]. Weight loss and gain may both occur. Causes of weight changes are not clear yet and different mechanisms have been invoked in determining them, particularly changes in energy expenditure and eating behavior [124,126–128]. Indeed, weight loss is a key feature of PD and a meta-analysis [129] has confirmed that PD patients have a significantly lower BMI than healthy controls. Weight loss may be present at diagnosis and it has been associated with disease progression [124,126–129]. In this process, a major role is likely played by the increase in energy expenditure associated with the onset and/or worsening of dyskinesias and rigidity [124,126,127] which is not fully compensated by an increase in energy intake [124] occurring with disease progression. Nonetheless, the impact of gastrointestinal dysfunction — namely dysphagia, sialorrhea and constipation — on energy balance should be always taken into account although the exact role still needs to be clarified [128,130,131]. Conversely, while body weight gain in the initial stages of the disease is likely dependent on dopaminergic treatment, which improves motor symptoms and could modulate eating behavior [128,131,132], in the advanced stages of the disease it is almost uniquely secondary to neurosurgical procedures [137]. Deep brain stimulation (DBS) is responsible for weight gain in the majority of patients due to reduction in energy expenditure — associated also with the reduction of motor complications (dyskinesias) — and changes in eating behavior [128,131,132,137]. The importance of weight management is multifaceted. Although weight loss primarily involves fat mass in patients with PD, with substantial sparing of skeletal muscle mass and low risk of sarcopenia [124,134,135], malnutrition has been associated with disease severity [126,127]. Besides, it is associated with an increase in the daily dose of levodopa (both total and per kilogram of body weight) which could induce or worsen dyskinesias. However, the prognostic role of weight loss in PD has to be determined. On the other hand, patients undergoing DBS should be actively monitored as weight gain is mainly of fat mass, significantly accumulating in the abdominal region [133]. While weight loss in PD patients is not usually associated with cardiometabolic complications [134], DBS induces metabolic disorders increasing the risk of metabolic syndrome [133]. Therefore, regular monitoring of body weight is recommended. Nutritional assessment should be conducted at least on a yearly basis and whenever the clinical conditions change.

PD patients should also undergo active monitoring of vitamin status. Low vitamin D levels have been associated with the risk of developing PD and serum levels are lower in PD patients than healthy controls [136,137]. A large case-control study has shown that, despite of higher food intake, the intake of vitamin D in PD patients is significantly lower than recommended dietary allowances [138]. Supplementation should be always considered as it seems to slow disease progression — at least in patients with high-risk genotype of the vitamin D receptor [139]. PD patients present also lower bone-mineral density (BMD) — which may further increase the risk of fractures associated with disease-related disability — than age-matched controls [140]. The only RCT available has shown that addition of vitamin D can reduce the risk of fractures in osteoporotic old PD patients by slowing the loss of bone mineral mass [141]. A reduction of homocysteine levels could also contribute to the improvement of BMD [142]. PD patients treated with levodopa show an elevation of homocysteine [143]. This is greater in patients on higher doses of levodopa and is due to levodopa methylation by catechol-O-methyltransferase (COMT) [144]. Accordingly, the concomitant use of COMT inhibitors (e.g. entacapone) may limit the raising of plasma levels, although the regulation is closely linked to vitamin B12 and folate status [143,144]. Interestingly, studies have shown that levodopa-treated PD patients have also lower circulating levels of folate and vitamin B12 [145,146]. On the other hand, administration of these vitamins is effective in reducing homocysteine levels [143,147,148] and should be always considered to prevent neuropathy [149,150] and other complications associated with hyper-homocysteinemia.

There has been growing interest in the role of oxidative stress in the neurodegenerative process. However, data on the association between antioxidants vitamins such as vitamin C, E, A and carotenoids are still inconclusive [151,152]. PD patients appear also to be characterized by reduced levels of coenzyme Q10 [153]. However, large randomized trials have shown that supplementation with either vitamin E or coenzyme Q10 showed no evidence of clinical benefit [154–156]. Therefore, the supplementation of these vitamins is not recommended. See supplementary data for Clinical Question 16.

4.2. Clinical Question 17: When and how should patients with PD be screened for dysphagia?

**Recommendation 24:**

All patients with Parkinson's disease with a Hoehn & Yahr stage above II or weight loss, low BMI, drooling, dementia or signs of dysphagia should be screened for dysphagia during an ON-phase.

**Grade of recommendation B – strong consensus (95% agreement)**

**Recommendation 25:**

A Parkinson’s disease specific questionnaire or a water swallow test with the measurement of the average volume per swallow is recommended.

**Grade of recommendation B – strong consensus (91% agreement)**
Commentary:

More than 80% of patients with PD develop dysphagia during the course of the disease [157,158]. Sometimes swallowing problems arise even early during the course of the disease [9]. Statistical risk factors for dysphagia in Parkinson’s disease are Hoehn and Yahr stage above III, weight loss, BMI below 20 kg/m², drooling or sialorrhea and dementia [157,159,160]. Although dysphagia is already reported in patients with a Hoehn & Yahr stage II, this does not seem to be clinically relevant in the sense of risk of aspiration and malnutrition. That is why it is recommended to start a regular screening from stage III on. However, if there are signs of dysphagia, such as coughing during meals or after drinking, pneumonia or subjective dysphagia, a screening and if necessary assessment should be performed irrespective of the stage of the disease.

A meta-analysis showed that the prevalence of oropharyngeal dysphagia based on subjective outcomes in PD patients is 35% and increases to 82% by taking objective measures of swallowing dysfunction into account [161]. This impressively demonstrates that in most PD patients oropharyngeal dysphagia is without obvious symptoms. Only 20–40% of PD patients are aware of their swallowing dysfunction, and less than 10% of PD patients report spontaneously about dysphagia [162,163]. In addition, silent aspiration is very common in PD [162–165]. This explains why it is necessary to actively screen PD patients for dysphagia. Dysphagia is associated with a high risk for decreased intake of food and fluids, aspiration and pneumonia [166]. Pneumonia is the most frequent cause of death in Parkinson’s disease and suspected to be substantially related to dysphagia [167]. Fear of aspiration and choking, food-modification and being dependent on others for food intake may alter also social and psychological wellbeing of patients with PD [168].

Even without obvious symptoms, dysphagia is clinically relevant and should be detected, i.e. should be screened for. A first step of screening can be a self-report questionnaire. Two standardized PD-specific questionnaires have been published for this purpose: the swallowing disturbance questionnaire (SDQ) and the Munich Dysphagia test-Parkinson’s disease (MDT-PD). With these questionnaires, PD-related dysphagia is identified with a sensitivity of 81% for both questionnaires, and a specificity of 82 and 71%, respectively [169,170]. The SDQ is more simple and easier to apply. The MDT-PD is able to detect milder forms of oropharyngeal dysphagia. An alternative or next step should be the application of a swallow-screening test. The usual water swallowing test as used in acute stroke patients has been shown to be non-predictive of severe oropharyngeal dysphagia in PD patients [159]. Although not yet sufficiently validated, experts recommend estimating the maximum swallowing volume as a screening test [171–173]. It uses a gradual increase of the volume of water that has to be swallowed. PD patients with a maximum swallowing volume below 20 ml are very likely to suffer from dysphagia. However, this test has only been evaluated in small study populations and has not yet been validated against instrumental tools [171–174]. A more simple and practical alternative is the measurement of the average volume per swallow [172]. Here, a defined volume of water (i.e. 100 ml) should be drunk in a usual manner and the time needed and the number of swallows is measured. The calculated volume per swallow is significantly lower in PD patients than in controls (13 vs 21 ml) [172,175,176]. Comparably, the volume that can be swallowed with one swallow is measured with the volume-viscosity swallow test in a stepwise manner (5, 10, 20 ml) for multiple consistencies [79]. This screening test is validated in PD patients against VFS. Thus the claimed 100% sensitivity for aspiration is in contrast with the data given by some studies, which report frequent silent aspiration in PD [159,164,177,178]. See supplementary data for Clinical Question 17.

4.3. Clinical Question 18: When and how should a clinical or instrumental assessment of dysphagia in PD be performed?

Recommendation 26:

All patients with Parkinson’s disease who were screened positive for dysphagia or demonstrate rapid deterioration of the disease, pneumonia or other signs of dysphagia should undergo an instrumental dysphagia assessment.

Grade of recommendation: GPP – strong consensus (100% agreement)

Recommendation 27:

The assessment should be done preferably with FEES, and if not available, with VFS. If instrumental dysphagia assessment is not available, clinical assessment should be performed instead.

Grade of recommendation: GPP – strong consensus (95% agreement)

Commentary:

Clinical assessment of dysphagia in PD patients is challenging and often delivers unreliable results. Silent penetration and aspiration is a frequent finding in PD and cannot be reliably detected by clinical assessment [164,165]. In addition, studies investigating the optimal way to perform a clinical swallowing examination in PD patients are lacking [179].

It has been shown that dopaminergic as well as non-dopaminergic mechanisms are involved in the development of dysphagia in PD [157]. Therefore, it is not predictable whether or not dopaminergic treatment will have a beneficial effect on dysphagia, which has to be tested where necessary [180].

FEES and VFS study (VFSS) are both considered gold standard for evaluation of PD-related dysphagia and should be the first choice assessment tool [157,181]. Considering the fact that the reliability of VFS in PD was questioned by one study [182], FEES entails also several practical advantages in comparison to VFS. It does not involve any radiation, it needs only minimal cooperation of the patients and may be performed as a bedside method [17]. Furthermore, FEES in PD may directly be utilized as a therapeutic measure, if performed in a feedback approach, described as video assisted swallowing therapy (VAST) [183]. In addition, high-resolution manometry is able to detect isolated or combined esophageal dysphagia in PD patients. It may even identify clinically silent swallowing impairment at an early stage of PD [184]. This method is often combined with impedance measurements, impedance manometry, which may increase the validity of the method [184–188].

Other techniques such as acoustical analysis of voice [189–191], acoustical analysis of swallowing or breathing sounds [192–194] lack high sensitivity or specificity and are not broadly available. The same is true for electromyography, which is of some value in the detection of the motor component of dysphagia in PD [195–198]. In addition, dynamic magnetic resonance imaging recently demonstrated some results but was not yet applied to PD patients [199,200]. See supplementary data for Clinical Question 18.

4.4. Clinical Question 19: Does the pharmacological treatment of PD improve dysphagia?

Recommendation 28:

Optimization of the antiparkinsonian treatment should be advised to ameliorate the motor symptoms that contribute to dysphagia in PD patients.
Grade of recommendation: B- strong consensus (100% agreement)

Commentary:

Levodopa and other antiparkinsonian drugs significantly improve the motor features of PD patients. However, there is little evidence about the effect of levodopa on swallowing function in patients with dysphagia. None randomized controlled trials have been design to explore this question, and only one meta-analysis [201] and one very well conducted systematic review of the literature [202] have been published on this topic.

In 2009, Menezes conducted a meta-analysis of five NRCT studies, assessing five outcome measures: oral transit time for thin fluids, solids, pharyngeal transit time for thin fluids and solids and presence of aspiration [201]. They concluded that levodopa intake was not associated with a significant improvement of swallowing dysfunction in PD patients. Some criticisms are published about this meta-analysis [203] (few studies, open-label, short in duration, small in sample size, not assessment of the effect of long duration levodopa treatment, inclusion of a variety of quality design studies, selection bias, poorly defined outcome parameters and dysphagia assessment tools that only explore one part of swallowing). Other authors as Lim et al. [204] concluded, in a very small study, that efficiency of swallowing can be reduced with levodopa treatment, while security of swallow remains unchanged. However, some authors have found improvements in swallowing function related to levodopa treatment [181,205], including one prospective study in de novo diagnosed PD patients, comparing 140 PD patients in their first year after dopaminergic treatment with 31 patients with no dopaminergic treatment [206]. The improvement in dysphagia probably is mediated through the improvement of motor symptoms (oral preparatory phase time, buccolingualoceric motor score, bradykinesia and rigidity of the tongue, and mandibular movement). Furthermore, the improvement of motor symptoms makes possible the adoption of compensatory postures that increase the airway protection during swallowing. Disease severity (based on the Hoehn and Yahr scale), on/off phase in which treatment was performed, and dysphagia assessment tool can be confounders to take into account in the design of such studies. See supplementary data for Clinical Question 19.

4.5. Clinical Question 20: Do side effects of drugs used to treat PD influence nutritional status?

Recommendation 29:

Side effects of drugs prescribed for PD might influence nutritional status. We recommend to monitor side-effects and nutritional status and to intervene on an individually tailored basis. For levodopa, specific attention should be given to homocysteine levels and vitamin B status.

Grades of recommendation: GPP — strong consensus (95% agreement)

Commentary:

There are several side-effects related to drugs prescribed for PD that might influence intake and nutritional status, including nausea, vomiting, abdominal pain, dyspepsia, constipation, weight decrease, dry mouth, diarrhea, anorexia and GI disorders [207–209]. These side-effects have been mentioned by patients to attribute to their weight loss, as well as changes in taste and smell of food [210]. Hence, in addition to the motor and non-motor symptoms of Parkinson's disease itself, some available treatments also contribute considerably to the changes in nutritional status [124]. The mechanism of drugs-related weight changes is still not well known and requires further investigation [126]. The use of levodopa may be associated with impaired nutritional status and risk for malnutrition. Increasing doses of levodopa and levodopa equivalent doses have also been found to be related to increased risk for malnutrition, as assessed with the Mini-nutritional Assessment (MNA). These associations were not seen for dopamine agonists [211]. Association between nutritional risk and levodopa has also been shown by others [130]. Research has indicated weight loss among levodopa users, especially in women (which might be due to higher levodopa dose per kg of body weight), and after starting levodopa treatment [212]. In this study, the magnitude of levodopa dose did not seem to be related to weight loss, and was mostly due to reduction in body fat mass [212]. BMI has also been shown to inversely correlate to levodopa treatment, pointing towards dose-dependent levodopa associated weight loss [213]. Yet, the true relationship between levodopa use and weight loss needs to be determined as it unknown whether higher levodopa use induce weight loss, or patients with more severe disease receive higher doses of levodopa per kg body weight. Indeed, in more advanced stages, higher doses of levodopa are required to improve the control of worsening motor symptoms. Higher (relative) doses in advanced stages are also associated to dyskinesias which, in turn, have been associated with weight loss [126].

Levodopa has been found to induce metabolic effects. The literature search included a study on metabolic effects (n = 10), showing that levodopa/benserazide (200 mg/50 mg) caused metabolic changes in adipose tissue and skeletal muscles disturbing lipid and carbohydrate metabolism. Hence, these results indicate that levodopa/benserazide does not reduce fat wasting through modulation of adipose tissue metabolism. Results pointed towards reduction in muscle glucose uptake, which might induce glucose intolerance [214]. Another small study in seven geriatric Parkinsonian patients showed increased plasma free fatty acids, glucose, growth hormone and cortisol after levodopa administration which were significantly higher compared to young controls, and only slightly higher compared to aged controls [215]. Long-term treatment with levodopa induces hypersecretion of insulin and growth hormone [124]. Levodopa challenges in PD patients with deep brain stimulation have shown to decrease REE in general, but significantly increase REE for those patients who had dyskinesias [216]. After the pharmacological change, lipid oxidation remained unchanged but glucose oxidation fell and fasting glycaemia was raised [216]. However, the true interrelationships between those factors need to be established.

Use of levodopa can cause hyperhomocysteinemia [217–220]. One study showed dependency upon vitamin B status as assessed by folate, vitamin B12, and vitamin B6. Patients on levodopa seem to have higher requirements for these vitamins to maintain normal homocysteine levels, and supplementation might be warranted [217]. Notably, many patients already take over the counter supplements which might explain the low prevalence of folate or cobalamin deficiency [218]. Risk factors for increased homocysteine levels include not solely higher levodopa use but also older age, longer disease duration, and lower serum levels of vitamin B12 and folate [218]. Although the clinical implication of hyperhomocysteinemia in PD patients is not well determined [219], in general, high homocysteine levels have been linked to cardiovascular diseases, dementia and depression [217–219]. In PD patients specifically, a higher relative risk for coronary artery disease has been shown with high plasma homocysteine levels [218]. See supplementary data for Clinical Question 20.
4.6. Clinical Question 21: Are rehabilitation therapies (behavioral, rheological, rehabilitation, neurorehabilitation) effective for the treatment of oropharyngeal dysphagia in PD patients?

**Recommendation 30:**

Rehabilitation treatment (adapting bolus characteristics, postural maneuvers and exercise programs) should be advised in PD patients with dysphagia in an individual manner, after a multidimensional assessment of the swallowing function. Other techniques such as a surface electrical stimulation, repetitive transcranial magnetic stimulation or video-assisted swallowing therapy have not yet enough evidence to make a recommendation.

**Grade of recommendation:** GPP — strong consensus (100% agreement)

**Commentary:**

There is not strong evidence in the literature for dysphagia intervention (compensatory and rehabilitative practices) in patients with PD. In 2001 a Cochrane systematic review of the literature was performed to examine the non-pharmacological therapies for dysphagia in PD patients [221]. None RCT or other forms of controlled trials were found and the authors concluded that there was insufficient evidence to support or to refuse swallowing therapies in PD. In 2009, Baijens identified five articles including rehabilitative and compensatory-based studies, identifying positive tendencies in favor of swallowing therapies, although these treatments targeted different aspects of physiology of swallow [222]. Michou et al. [168] reviewed in 2010 the current evidence, and also concluded that clinical practice in this area lacks research evidence. In 2014, van Hooren et al. [223] published a systematic review of the literature searching for effective treatments for dysphagia management in PD patients, including surgical interventions, bolus modification, neuromuscular electrical stimulation, postural and airway protective maneuvers, and pharmacological interventions, and they found some evidence for theatory strength training and video-assisted swallowing therapy. However, rehabilitative approach could possibly have greater potential in the long-term to increase swallowing safety and improve quality of life for PD people with dysphagia [224], although more research is needed to determine the most effective therapy, the duration of the treatment, therapy intensity, timing on therapy start, and the maintenance of improvements.

**Adapting bolus characteristics:** Adapting bolus characteristics such a consistency or volume can change certain parameters of swallowing safety. Troche et al. [225] compared, in a short trial, the effect of thin versus thickened consistencies on swallowing timing and penetration-aspiration scores in patients with PD. They concluded that pudding-thick liquids resulted in significantly higher oral transit time and number of tongue pumps than thin liquids, however they found significantly lower penetration-aspiration scores for pudding-thick liquids, so a safer swallow for people with PD.

**Postural maneuvers:** Logemann et al. [226] conducted a large study into compensatory approaches for dysphagia management in PD patients, comparing sequentially three strategies commonly used to treat aspiration risk: chin-down posture, nectar-thick fluids and honey-thick fluids. The study included 277 patients with PD and 135 with PD and dementia. For all patients group the chin-down posture was the least effective at preventing aspiration, and honey-thick liquids were the most effective. Overall, participants had significantly more episodes of aspiration using the chin-down posture with thin liquids than when taking nectar-thick liquids or honey-thick liquids. Unfortunately, 39% of patients with PD and 50% of patients with PD and dementia aspirated on all three interventions. Robins et al. [227] explored the efficacy of the mentioned three strategies to prevent aspiration pneumonia in a 3 months follow-up study, and they concluded that neither chin-down posture nor thickened fluids are superior in preventing adverse outcomes of dysphagia in participants with PD or PD plus dementia.

**Exercise programs:** Exercise program such as expiratory muscle strength training (EMST) have demonstrated improvement in cough and swallow function in PD patients. Individuals that received active EMST for 4 weeks presented with improved penetration/aspiration scores, and improved hypolaringeal complex function (excursion time and displacement) as compared with both their pretreatment assessment [228] and with placebo-controlled group [229]. Argolo et al. [230], in a short prospective cohort study, evaluated the effect of an oral motor exercise program supervised by a speech language therapist. They performed training with different amounts of thin and thick liquids, puree, and soft solid foods for 5 weeks. The authors found an increase in the strength and range of motion of the mouth, larynx and pharynx, improvement in the oral control of the bolus, coordination between breathing and swallowing and airway protection using a VFS. Different structured swallowing programs have been demonstrated, their efficacy on improving neuromuscular control of oral phase and tongue function during oral and pharyngeal phases of swallowing, such as intensive Lee Silverman Voice Treatment in a non-RCT of 1 month of duration [231].

**Other interventions:** Thermal-tactile stimulation of the anterior faucial pillars has been investigated to improve swallow timing in people with PD. Fifteen PD patients with oropharyngeal dysphagia and pharyngeal swallow delay detected by VFS were submitted for thermal-tactile stimulation [222], and the technique was effective for reducing pharyngeal transit time and total transit time, but not to reduce oral transit time. Nevertheless, it is not clear that this technique will be associated with a safer and more efficient swallow in PD patients.

Surface electrical stimulation of the submenton region has been used as adjunct to traditional logopedic dysphagia treatment in PD patients. Baijens et al. [233], in a sequential assignment study with 90 PD patients, explored the effect of motor-level surface electrical stimulation or sensory-level surface electrical stimulation together with logopedic swallowing therapy, and they compared the results with a control group with only traditional logopedic therapy. All the treatments sessions and the examinations were performed during the “on” motor phase after the intake of antiparkinsonian medication. After 15 days of treatment, the authors found no statistically differences in VFS or FEES variables between the three treatment groups.

Neuromuscular electrical stimulation of the suprahoid musculature has been explored combined with traditional logopedic treatment [234] in a RCT including 109 PD patients assigned to three intervention groups in a consecutive manner. The study shows positive effects of dysphagia therapy in patients with PD in all three groups of intervention, but only slight non-significant differences between groups have been found after one month.

Repetitive transcranial magnetic stimulation, a neuro-rehabilitation non-invasive technique, has been used to modulate neural activity in targeted focal brain regions. Murdock et al. [235] showed in a controlled study, that transcranial stimulation in the left tongue area of the motor strip improves the maximum velocity of tongue movements and distance of tongue movements. VAST is based on a visual cueing mechanism to improve motor and coordination skills in swallowing. Manor et al. [183] evaluated this treatment in 42 PD patients, in a RCT comparing compensatory...
and conventional swallowing exercises with or without VAST during 4 weeks. After VAST, the food residue in the pharynx and subjective patient-self-reports about dysphagia significantly improved compared with conventional therapy alone.

Other treatments as botulinum toxin-A injections have been effective for treating sialorrhoea in PD, but no effects on swallowing has been reported. See supplementary data for Clinical Question 21.

4.7. Clinical Question 22: Is there a role for protein redistribution and/or low-protein diet in PD patients on levodopa treatment?

Recommendation 31:

In addition to advising PD patient to take levodopa medications at least 30 min before meals, we recommend advising those experiencing motor fluctuations to try complying with a protein-redistribution dietary regimen to maximize levodopa absorption and efficacy.

Grade of recommendation B – strong consensus (90% agreement)

Commentary:

Levodopa is the most effective drug in the treatment of PD. Due to its chemical structure it competes with dietary large neutral amino acids for intestinal absorption and transport across the blood–brain barrier. Therefore, all patients are advised to take their levodopa-containing medications about 30 min before meals to avoid interactions [124,236]. However, levodopa-responsive PD patients experiencing motor fluctuations (sudden/unpredictable changes from phases of optimal motor function or mild dyskinesia ['ON’ state] to phases in which PD motor symptoms reappear ['OFF’ state]) should be recommended to comply with controlled-protein dietary regimens to maximize levodopa absorption and efficacy [236,237]. Redistribution of protein intake throughout the day (low-protein breakfast and lunch and consumption of a second-course — with no quantitative restrictions in terms of protein — only at dinner) was found to improve motor function and disability and to increase the duration of “ON” state [236], particularly when the intervention is proposed to patients in the early stages of PD and with onset of PD in younger age. Furthermore, a good-quality randomized, cross-over, single-blind, trial has also shown that the use of low-protein foods designed for patients with chronic renal failure [238] are helpful in achieving protein redistribution. However, patients should undergo active monitoring. This could enable avoiding dropout associated with potential complications including weight loss, micronutrients deficits, hunger before dinner and dyskinesias [236,239]. Particularly, patients experiencing the onset or worsening of dyskinesias may require reduction in levodopa doses [236]. One of the objectives of redistribution is to meet daily protein requirements, which could be set to 0.8—1.0 g/kg of body weight. Although this advice may appear in contrast with recent recommendations [240], no adverse effect of protein-redistribution regimens on body composition (e.g. loss of muscle mass) have been reported [238], at least in the short term. Nevertheless, data on protein redistribution diet in very old PD patients are scant and potential benefits should be balanced along with clinical conditions (e.g. comorbidities, frailty status, etc.) and its feasibility.

The role of strict low-protein diet has not been investigated in good-quality clinical trials and there is no evidence supporting this dietary regimen [236]. Besides, despite recent interest [241], there is no evidence supporting the use of gluten-free or plant-food-based diets in PD patient with motor fluctuations. The dietary management of other gastro-intestinal problems (delayed gastric emptying and constipation) impairing levodopa efficacy may be also beneficial as these can result in reduced bioavailability and higher requirements of levodopa [124,138].

Similar recommendations can be provided to PD patients treated with continuous duodenal duodopa. Patients should be advised to distribute food intake throughout the day and to divide the protein intake. In case of low-infusion-rate continuous EN by gastric tube feeding we do not give any restrictions but it is advisable to concentrate it during the night hours if possible in order to limit interactions. Finally, in tube-fed patients still treated with oral formulations of levodopa-containing medications we could suggest the interruption of enteral nutrition for at least 1 h before and 30—40 min after drug administration. See supplementary data for Clinical Question 22.

4.8. Clinical Question 23: Does medical nutrition therapy improve quality of life or survival in patients with PD?

Recommendation 32:

We advise that PD patients should receive medical nutrition therapy to improve well-being and quality of life. Medical nutrition therapy should be tailored to individual requirements.

Grade of recommendation: GPP – strong consensus (100% agreement)

Commentary:

Quality of life (QoL) is related to nutritional status; research shows that PD patients who are moderately malnourished have lower quality of life than patients who are well nourished [242] and MNA scores are inversely correlated to quality of life domains, especially mobility and emotional well-being domains [243]. There is however very limited literature on the effectiveness of medical nutrition therapy on the improvement of the quality of life or survival of patients with PD. Individualized nutritional information provided by a dietician with weekly telephone contact did not show improvement in quality of life compared to written information only [242]. Two years supplementation of creatine has been shown to have some beneficial effects for mood over placebo treatment, but did not influence overall quality of life or disease progression [244]. A review on the use of antioxidants and supplements has shown a limited role for treatment with some benefit for CoQ10 supplementation on Unified Parkinson Disease Rating Scale (UPDRS) activity daily living scores, although this seemed inconsistent among studies [245]. Finally, since food-derived amino acids compete with levodopa for entry into the brain across the blood–brain barrier, protein redistribution diets have been proposed and demonstrated to improve the efficacy of levodopa. Positive effects have been found not only on motor symptoms but also on disability score [236], both which have been linked to reduced QoL. However, ad-hoc evaluations of QoL in PD patient adhering to protein redistribution diets are not available. The effect of medical nutrition therapy on survival in PD patients has not been studied, which urges the need for intervention trials on this topic. See supplementary data for Clinical Question 23.

4.9. Clinical Question 24: Do patients with PD who suffer from constipation benefit from diet therapy?

Recommendation 33:

PD patients with constipation can benefit from the use of fermented milk containing probiotics and prebiotic fiber in addition to common dietary advices aimed at increasing the intake of water and fiber.
5. Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory and autoimmune disease of the central nervous system, leading to widespread focal degradation of the myelin sheath, variable axonal and neuronal injury, and disability in young adults. From the clinical point of view, there are at least two main forms of the disease: the relapsing-remitting MS (RRMS, concerning about 85% of clinical cases) and the primary-progressive MS (PPMS, affecting about 15% of the clinical cases). In RRMS, the conduction of nerve impulses along the axon of the neuron may be affected during an acute inflammatory phase (relapse), but tend to improve with healing during the remission phase. Over time, relapses cause extensive damage and scarring of the myelin sheath with progressive loss of neuronal function. Pathogenesis of PPMS is characterized by progressive neurological damages rather than relapses and remissions. The cause of MS is unknown, but research suggests that genetic, immunological and environmental factors, such as a common virus, may all be involved in a complex etiology.

Commentary:

Dysphagia can be one of the most important complications of MS that could affect nutritional status [252]. Dysphagia in MS usually results from brain stem involvement, and is often accompanied by speech difficulties.

5.1. Clinical Question 25: Is there a role for a dietary prevention of MS?

Recommendation 34:

We suggest a diet lower in saturated fat and higher in polyunsaturated fatty acids from food sources for the prevention of MS.

Grade of recommendation: B — strong consensus (91% agreement)

Commentary:

Dietary factors have repeatedly been studied as a way to prevent the occurrence of MS, without significant positive results [253]. The main constituents of the diet that have been studied as a way to prevent the occurrence of MS and other demyelinating diseases are specific dietary patterns, the type of dietary fat, with emphasis on polyunsaturated fatty acids (PUFA) intake, vitamin D, other vitamins, minerals and trace elements and gluten [254].

Epidemiological studies have suggested an association between the incidence of MS and the intake of saturated fat of animal origin. In 1950 Swank was the first researcher to suggest a positive link between MS and high saturated fat intake [255]. According to his study, the amount of saturated fat consumed during the Second World War was lower in northern countries, i.e. Norway, Denmark, Sweden, Switzerland, Holland, Belgium and England and so was the incidence of MS. In later studies he also noted that countries with higher consumption of polyunsaturated fat intake and lower of saturated fat, such as the coastal areas of Norway had lower incidence of MS [256].

Polyunsaturated fatty acids intake was of major interest and several pathophysiological pathways were suggested for omega 3 (ω-3 or n-3) and omega-6 (ω-6 or n-6) fatty acids, based on their immunoregulatory, anti-inflammatory and anti-coagulant properties as well as the significant role of these fatty acids on the Central Nervous System (CNS) as compounds of the myelin membrane [256,257]. In a very recent study, higher consumption of n-3 polyunsaturated fatty acids from fish origin was associated with lower risk of first clinical diagnosis of MS [258]. However, there is a limited number of studies for the direct effect of polyunsaturated fatty acids supplementation on the risk of developing MS and other demyelinating diseases. In patients with MS there are several trials testing the efficacy of the supplementation of n-3 and n-6 fatty acids on disease activity measured with magnetic resonance imaging, relapse rate and disability progression (see Clinical Question 26). The results of the majority of the studies are either neutral regarding the effect of these fatty acids on the primary outcome parameters [259], or the quality of the positive studies is low, not allowing extracting safe conclusions [260]. The negative results of the supplementation of PUFA in manifest MS however, do not exclude some preventive efficacy [261].
Recommendation 36:

We recommend sufficient dietary vitamin D intake and adequate sunlight exposure that ensures adequate vitamin D levels for the prevention of MS. In cases of low vitamin D intake, low sunlight exposure and subsequent low levels of vitamin D, dietary supplementation is recommended.

Grade of recommendation: B – strong consensus (91% agreement)

Commentary:

The hypothesis that MS is associated with low sunlight exposure and subsequently low vitamin D3 levels was based at first on the geographical variability of its prevalence [262–264]. Furthermore, epidemiological studies have suggested a link between sunlight and vitamin D3 and MS [265], a finding that has been corroborated in observational and case–control studies. More specifically, in a study on 187,563 women in USA, the risk of MS was inversely associated with the vitamin D intake by supplements, a relation which failed to reach significance when vitamin D from food was assessed [266]. This association was further confirmed in a case–control study of 148 cases and 296 controls where 25-hydroxyvitamin D3 plasma concentrations were inversely associated with the MS risk, particularly if the levels had been low before the age of 20 years [260,264].

Recommendation 37:

We do not recommend vitamin B12 supplementation as a way to prevent MS.

Grade of recommendation: 0 – strong consensus (95% agreement)

Commentary:

It is well established that vitamin B12 deficiency causes neurodegeneration of sensory and motor neurons, a condition that is reversed when deficiency is corrected. Above that, no neuroprotective effects of vitamin B12 supplementation have been documented. Moreover, the hypothesis linking MS and vitamin B12 deficiency has not been confirmed [260,267].

Recommendation 38:

We do not recommend vitamin C supplementation as a way to prevent MS.

Grade of recommendation: B – strong consensus (95% agreement)

Commentary:

Ascorbic acid is a well-known antioxidant, protecting cells against oxidative stress. High levels of vitamin C intake though have not been proven beneficial neither for neurodegenerative nor cardiovascular diseases [260].

Recommendation 39:

A gluten free diet in order to prevent MS is not recommended.

Grade of recommendation: B – strong consensus (100% agreement)

Commentary:

The connection of gluten and MS was mainly based on the hypothesis that gluten hypersensitivity may contribute to neuro-immunological diseases based on results of brain magnetic resonance imaging (MRI) from celiac disease patients that had similarities with MS patients [260]. This hypothesis though was not supported by further studies, in which neither the anti-gliadin antibodies nor morphological changes in the gut mucosa were reported in patients with MS [268–270]. Furthermore, the withdrawal of gluten containing foods from the diet of MS patients was not found to have any significant positive effect [271].

Recommendation 40:

Prevention of obesity in adolescence and early adulthood is recommended for the prevention of MS.

Grade of recommendation B – strong consensus (100% agreement)

Commentary:

Overweight and obesity during adolescence and early adulthood seem to contribute to overall risk of development MS. Excess adipose tissue may have a negative impact on vitamin D metabolism and bioavailability, resulting in lower blood levels of 25(OH) vitamin D levels in obese compared to healthy individuals [272-273]. In the Nurses’ Health Studies (NHS/NHSII) it was reported those women who were obese at the age of 18 (BMI ≥ 30 kg/m²) had a two-fold increased risk of developing MS compared to women with BMI between 18.5 and 20.9 kg/m² (RR = 2.25, 95 %CI: 1.5–3.37). Obesity in younger ages also was correlated with increased risk of MS but after adjusting for body size at these ages the significance remained for women being obese at the age of 20 years (RR = 1.96, 95 %CI:1.33–2.89) [274]. Concluding, obesity in adolescence and early adult life may increase the risk of MS and its prevention may contribute to the reduction of its risk [275,276]. See supplementary data for Clinical Question 25.

5.2. Clinical Question 26: Can medical nutrition therapy decrease the rate and severity of relapses in MS patients?

Literature review regarding this topic focused the attention on the role of some vitamins, specially vitamin D and omega fatty acids as potential modulators of the disease.

Recommendation 41:

There is insufficient evidence to recommend vitamin D therapy in MS patients. There is no clinical evidence on the effects of either vitamin D compared with placebo or high-dose vitamin D compared to low-dose on the relapse rate of patients with MS.

Degree of recommendation: B – strong consensus (100% agreement)

Commentary:

In the latest years, the relation between vitamin D and MS has generated an enormous interest. The relationship between geographical differences in the prevalence of MS, sun exposure and vitamin D metabolism have been studied. Relapses of the disease occur more frequently in winter when vitamin D levels are lower.
Vitamin D exerts many immunomodulatory effects, increases lymphocyte proliferation and reduces the production of pro-inflammatory cytokines. In the epidemiological study US-American Nurses’ Health Study [277], women who took vitamin D supplements had a lower risk of MS, although it is difficult to extract the results due to other vitamins in the diet or vitamin supplements. Ascherio et al. [278] demonstrated, in a large multicenter randomized trial designed to evaluate the impact of early-versus delayed-interferon beta-1b treatment in patients after a first event suggestive of MS, that higher levels of 25-vitamin D predicted reduced MS activity (relapses and disability) and led to a slower rate of progression at 24 months.

Unfortunately, the studies that evaluate the effect of vitamin D are prone to many sources of bias (selection bias due to diet or sun exposure, reverse causation due to the disease, and effect of the skin type or genetic factors) [279,280].

One National Guideline (NICE) has addressed the topic of the clinical evidence of pharmacological treatment of vitamin D in patients with MS [281]. A recent systematic review of the literature has also been published [282]. Four studies have assessed the effect of vitamin D versus placebo on the disease relapses over follow-up time or on the annualized relapse rate [283–286]. Burton et al. [283] assessed, in an open-label 52-week duration RCT, the effects of high doses of vitamin D (40.000 IU/day for 28 weeks, followed by 10.000 IU/day over 28 weeks). After the trial, mean annualized relapse rate in treatment patients decreased although the results were not statistically significant. The proportion of treatment patients experiencing relapses during the trial was 0.16 vs 0.37 in the control group (p = 0.09).

Shayannejad et al. [283] studied the effect of low dose vitamin D in combination with current disease-modifying therapy on the prevention and progression of relapsing-remitting MS, in a double-blind placebo-controlled study including consecutive 50 patients. They were randomized to receive 12 months escalating doses of calcitriol up to 0.5 μg/day or placebo. They defined acute relapse as the appearance of a new neurological symptom or severe deterioration in a preexisting symptom that lasted for at least 24 h in the absence of fever/infection and caused an increase of at least 1 point in the Expanded Disability Status Scale (EDSS). After the trial, the mean relapse rate decreased significantly in both groups. The authors concluded that there is no evidence of an effect on the odds of remaining relapse-free during the first 12 months of therapy in patients who received vitamin D compared to those who received placebo.

Kampman et al. [285] performed a 96-week RCT to assess the effect of vitamin D3 supplementation (20.000 IU weekly) or placebo on bone mineral density in 68 patients with MS. As a secondary endpoint, they assessed the effect on annualized relapse rate. After the trial, there was no significant difference between groups in annualized relapse rate (absolute difference 0.10, 95% CI –0.07–0.27, p = 0.25). The authors concluded that supplementation with 20.000 IU vitamin D3 weekly did not result in beneficial effects on the relapse rate in MS patients.

Soili-Hänninen et al. [286] evaluated the effect of 20.000 IU of vitamin D3 weekly for 1 year in a double blind, placebo-controlled randomized trial including 66 MS patients treated with interferon β-1b for at least 1 month. The primary endpoint was disease activity measured by MRI scan. As a secondary endpoint, they assessed the annual relapse rate in both groups. After the trial, the annual relapse rate decreased during the study in both treatment arms (from 0.49 [284] assessed in an open-label study on 20 high-dose vitamin D versus placebo in relapsing remitting MS, patients with chronic progressive disease provided another important bias in the results of any nutritional treatment in the relapses of MS. The selection of the placebo is also a matter of discussion. Some PUFAs intervention studies used olive oil as a placebo, and evidence demonstrates that oleic acid is not an inert substance. Also, recently published NICE Guidelines assessed the clinical evidence of omega-3 and omega-6 fatty acids [281] on the evolution of MS patients.

Omega-6 fatty acids: Some authors have reported low levels of linoleic acid in blood, in the erythrocyte membrane and
cerebrospinal fluid of MS patients. There have been several small placebo-controlled studies evaluating intervention with [261] linoleic acid (obtained from sunflower oil). Although studies have been conducted with small samples, none of them has been shown any effect on relapse rate or degree of disability [291]. In a meta-analysis including 3 studies with 87 patients and 85 controls, some benefit was observed in the group of patients with moderate disabilities or short disease duration at baseline, in terms of reduced disability progression and reduced severity and duration of relapses [292]. The results in the group of severely disabled patients are not as consistent. A 2012 Cochrane review [293] including 6 randomized controlled trials investigating PUFAs effect on disease progression assessed 794 patients, and they concluded that PUFAs seem to have no major effect on the main clinical outcome in MS (disease progression), but they may tend to reduce the frequency of relapses over two years. However, the data that are available are insufficient to assess a real benefit or harm from PUFAs supplementation.

**Omega-3 fatty acids:** docosahexaenoic acid (DHA) is present at high concentration in the brain, but its levels decrease in MS patients. Both eicosapentaenoic acid (EPA) and DHA are found in high proportion in fish oil and show remarkable anti-inflammatory, antithrombotic and immunomodulating activities and also exert important effects on gene expression. For this reason, n-3 fatty acids exert a number of neuroprotective effects. There are insufficient data to confirm any beneficial effect of omega-3 fatty acids in patients with MS, although some studies with small samples have shown some promising results. In a large intervention study with 292 patients randomized to take fish oil (1.7 g of EPA and DHA 1.1 g per day) or olive oil as placebo, no significant differences were found between the two groups with regard to the frequency, duration or severity of relapses [294]. See supplementary data for Clinical Question 26.

### 5.3. Clinical Question 27: Does medical nutrition therapy improve nutritional status in MS patients?

**Recommendation 43:**

We recommend early detection and treatment of the causes of malnutrition by a multidisciplinary team in patients with MS.

**Grade of recommendation:** GPP — strong consensus (100% agreement)

**Recommendation 44:**

We strongly recommend the provision of dietary advice for the prevention and treatment of nutritional problems in patients with MS. In patients unable to meet their nutritional needs by food intake the use of oral nutritional supplements should be considered.

**Grade of recommendation B — strong consensus (100% agreement)**

**Commentary:**

Unintentional weight loss and malnutrition are common in patients with MS, even though the data regarding malnutrition prevalence and its treatment in patients with MS are scarce [295,296]. One of the most important cause of malnutrition in MS patients is dysphagia, limiting nutritional intake and deteriorating nutritional status of the patients [251].

Malnutrition has also been shown to impair immune system and strength, to induce fatigue and impair muscle function, affecting mental function, respiratory muscle strength and increase the risk of infections. The prevention of malnutrition is of vital importance in patients with MS as it can compound existing symptoms, such as muscle dysfunction, fatigue and muscle spasms [295]. According to a Cochrane review the evidence supporting the effectiveness of interventions on the management of fatigue and/or weight loss in advanced stages of progressive illnesses such as MS are lacking [297]. Nevertheless, the adequate provision of nutrients by diet and/or medical nutrition therapy should be considered in patients with MS in order to prevent and correct malnutrition and nutrient deficiencies.

Nutritional screening and assessment of the nutritional status of the patients with MS with appropriate screening and assessment tools is necessary, with the input of the patient and the caregivers. Medical nutrition therapy in patients with MS requires a multidisciplinary approach. The participation of a neurologist, a nutritionist/dietitian, a speech and language therapist for the evaluation of swallowing ability, physiotherapist for the evaluation of eating posture, occupational therapist to evaluate the need of specific cutlery and a nurse is of vital importance in order to perform a comprehensive evaluation of the etiology of malnutrition in order to ensure the early detection of problems affecting sufficient nutrient intake [251,295]. The efficacy of dietary advice has been evaluated in several systematic reviews for the treatment of disease-related malnutrition. Dietary advice alone or with ONS may improve weight, body composition and muscle functionality, even though no positive results on survival by either interventions was observed [298–300].

Although there is a lack of trials focusing on the effectiveness of ONS on nutritional status of malnourished patients with MS, the efficacy of ONS in chronic illness in the community and hospital setting has been evaluated by several systematic reviews [298,299,301,302]. ONS use in the community has been identified as a cost-effective way of treating malnutrition, producing a neutral or an overall cost advantage, in combination with clinically relevant outcomes [302,303]. See supplementary data for Clinical Question 27.

### 5.4. Clinical Question 28: Can medical nutrition therapy improve survival in MS patients?

**Recommendation 45:**

We have no direct evidence about the effect of medical nutrition therapy on survival in MS patients. More research is needed to answer this gap of knowledge.

**Grade of recommendation:** GPP — strong consensus (100% agreement)

**Commentary:**

To date, there is no RCT that has assessed the influence of medical nutrition therapy in the survival of malnourished patients with MS that cannot meet their nutritional requirement with their usual diet. Some authors have evaluated prognostic factors for mortality in MS patients. Chruzander et al. [304] evaluated in a population-based study in Stockholm, the effect of some personal and disease-specific factors on mortality at 10 years’ follow-up, and they detected higher age at diagnosis (>51 y), progressive disease course and depressive symptoms as negative prognostic factors for survival. Similar results are confirmed by Kinqwelt et al. [305] with regard to age at diagnosis and progressive form of the disease. Scalfari [306] analyzed data of published large cohorts’ registries, and also found higher age at diagnosis as a negative prognostic factor for mortality. None of the mentioned studies analyzed any nutritional data as a
prognostic factor for mortality in MS patients. From indirect data, some authors have found that respiratory infection and sepsis are the most frequent MS–related causes of mortality [307], and we can hypothesize that dysphagia and or malnutrition can be involved as a causative factor. However, there is a lack of intervention studies to demonstrate the effect of medical nutrition therapy on survival in MS patients.

5.5. Clinical Question 29: Are there specific methods for screening and clinical diagnosis of OD in MS?

Dysphagia is a common symptom in MS patients, and can be the consequence of several potential factors such as involvement of the corticobulbar tracts, cerebellar and brainstem dysfunctions, lower cranial nerves paresis and cognitive impairment, all of which can impair swallowing physiology. Dysphagia can cause severe morbidity in MS patients, increasing the risk of dehydration and aspiration pneumonia and reducing the quality of life and increasing mortality. Prevalence of dysphagia in patients with MS ranges between 10 and 90% of patients, depending on the method used to evaluate the swallowing problem and the population included in the study. A recent meta-analysis [10] showed that the pooled prevalence of 12 studies using subjective methods (different dysphagia questionnaires and only one water swallowing questionnaire) is of 36% (95% CI 31–42). However, the pooled prevalence of objective methods (instrumental measurements, 3 studies VFS and one study FEES) is of 81%. Nevertheless, there was substantial heterogeneity across subjective and objective prevalence estimate. Several studies reported that the prevalence of dysphagia was related to the disability and the duration of the disease [11,308,309], while other studies reported that dysphagia can be present in MS patients with an Expanded Disability Status Scale lower than 2.5 (low disability) [310].

**Recommendation 46:**

MS patients should be screened for dysphagia early in the course of the disease, especially if they have cerebellar dysfunction. The screening should be repeated at regular intervals depending on clinical situation. We have not enough evidence to recommend one specific screening method for dysphagia in this population.

Grade of recommendation: GPP — strong consensus (95% agreement)

**Recommendation 47:**

MS patients should be screened routinely for dysphagia over the course of the disease, although we have not sufficient evidence to recommend the timing. Patients with severe disabilities, cerebellar dysfunction and long disease duration are the highest risk patients.

Grade of recommendation: GPP — strong consensus (96% agreement)

**Recommendation 48:**

Instrumental exploration of dysphagia should be performed in MS patients with high risk for dysphagia (severe disabilities, cerebellar dysfunction and long disease duration), or dysphagia symptoms. We have not sufficient evidence to recommend one specific method for diagnosis.

Grade of recommendation: GPP — strong consensus (100% agreement)

**Commentary:**

Clinical screening of dysphagia: A clinical questionnaire to detect patient-reported dysphagia in MS patients was designed by Bergamaschi et al. [311]: the Dysphagia in Multiple Sclerosis (DYMUS) questionnaire. The survey includes 10 questions that allow the assessment of dysphagia for solids and liquids. DYMUS questionnaire was initially performed in a cohort of 226 consecutive outpatients and later validated in a very large group of consecutive MS patients during routine checkups outside relapses [312,313]. It identified 92% of patients complaining for swallowing problems. In asymptomatic patients, the DYMUS questionnaire identified 14% of patients that should be subjected to further, more specific investigations. The questionnaire was abnormal in 31% of patients. The patients that reported dysphagia with the test had higher EDSS score and longer disease duration. The results of the DYMUS questionnaire correlated positively with the penetration–aspiration scale measured by FEES in a small group of consecutively hospitalized MS patients [314]. To date, the DYMUS questionnaire has not been formally validated with an instrumental tool to evaluate the sensitivity and specificity of dysphagia in MS patients. Other bedside clinical tests for the assessment of dysphagia are not validated specifically for screening of dysphagia in MS patients. Clave et al. [79] only included 4 MS patients in their validation of the volume-viscosity swallow test. De Pauw et al. [308] reported the results of the questionnaire of the Johns Hopkins Swallowing Centre in 68 of 73 MS patients with permanent dysphagia (defined as dysphagia outside an acute relapse), and they found that the most frequent symptoms were altered feeding habits (92%), coughing and choking during meals (58%), food sticking in throat (32%) and difficulty managing secretions (32%). Twelve per cent of patients had history of pneumonia. Levinthal et al. [315] explored dysphagia prevalence using the MD Anderson dysphagia inventory in a cohort of 218 consecutive patients recruited to participate either during routine follow-up clinic visits or during scheduled visits for drugs infusions, and reported a prevalence of dysphagia in 20% of patients. The swallowing functions of 101 consecutive MS patients were screened by the Northwestern Dysphagia Patient Check Sheet by Poorjavad [252] and 31.7% were classified as having dysphagia. Pharyngeal stage disorders were the most common observed impairment (28.7%) and aspiration, oral stage disorders, and pharyngeal delay were observed in 6.9%, 5%, and 1% of patients, respectively. Patients with dysphagia had significantly longer disease duration, more neurological impairment in cerebellar functional system and more neurological disability as measured by ESSD scores. Thomas et al. [316] explored dysphagia in a group of 79 MS patients consecutively admitted to the hospital using a water test (150 ml), and found positive screening for dysphagia in 43% of patients. Abnormal swallowing was associated with several factors including abnormal brainstem/cerebellar function, disability, vital capacity, and depression score.

Instrumental diagnosis: Clagagno et al. [11] reported the results of FEES in 143 consecutive patients with primary and secondary progressive MS who underwent for neurological rehabilitation, and they found dysphagia in 34% of patients. In this study, dysphagia risk was related with severe brainstem impairment (OR 3.24; 95% CI 1.44–7.31) as compared with patients without severe brainstem impairment. Severity of the illness was also associated with risk of dysphagia (OR 2.99, CI 1.36–6.59), but not with duration of the disease. Fernandes et al. [317] explored a cohort of 120 MS patients with FEES, and they reported a 90% prevalence of dysphagia, more frequent in secondary progressive and primary progressive forms of the disease, and related with involvement of cerebellar, brainstem and mental functions on the Functional Disability Scale and also...
with worse Expanded Disability Status Scale (EDSS) scores. The study of Alfonsi [314] found a 53% of abnormal FEES in a cohort of 26 MS patients. De Pauw et al. [308] explored with manouelfluoroscopy 30 of the 73 MS patients with permanent dysphagia in their study, while only the patients with an EDSS higher than 7.5 showed abnormalities of the pharyngeal phase (mostly hypopharyngeal hypocontractility and reduced opening of the upper esophageal sphincter).

Two studies explored dysphagia with VFSS in MS patients. Wiesner et al. [318] found videofluoroscopic abnormalities in 55% of 18 consecutive MS patients, including 75% of patients absolutely asymptomatic with regard to swallowing. Terre-BolIart et al. [319] reported a prevalence of 83% of VFSS abnormalities in 23 MS patients controlled in a neurorehabilitation unit. In 52% of patients with dysphagia there was some change in the swallowing safety, and 40% of them were silent aspirators. Electrophysiological evaluation of dysphagia has been performed by Alfonsi [314] and Beckmann [320] in 26 and 51 patients, respectively. They found a high prevalence of electrophysiological abnormalities in asymptomatic patients (subclinical dysphagia), that can be unmasked performing a sequential water swallowing test during electrophysiological evaluation of swallowing. Electrophysiological evaluation of dysphagia can be a promising exploration to detect early dysphagia. All these results emphasize the importance of assessment and management of swallowing function in MS patients, particularly in patients with a high EDSS score, more severe cerebellar dysfunction, and long disease duration. See supplementary data for Clinical Question 29.

5.6. Clinical Question 30: What are the effects of behavioral, rheological and rehabilitation treatments for OD in patients with MS?

Recommendation 49:

We recommend in MS patients with dysphagia the use of modified consistency foods and fluids to ensure safe swallowing, according to the individualized needs of the patients.

Grade of recommendation GPP – strong consensus (96% agreement)

Recommendation 50:

No disease specific recommendation can be provided for the behavioral treatment of dysphagia in patients with multiple sclerosis due to lack of evidence. Therefore, general recommendations for dysphagic patients should be followed.

Grade of recommendation GPP – strong consensus (100% agreement)

Recommendation 51:

We recommend EN therapy in dysphagic patients unable to cover their nutritional needs orally. In patients with MS and other chronic neurological disorders PEG should be chosen as a method of delivery of EN.

Grade of recommendation B- strong consensus (96% agreement)

Commentary:

Dysphagia in multiple sclerosis has been found to be more frequent than it was previously thought, affecting almost one third of the patients [10,308]. Permanent dysphagia may already develop in mildly impaired MS patients but becomes a rather frequent finding in MS patients with moderate or severe disability [308]. Dysphagia is a serious condition, affecting the ability of the patient to fully cover his nutritional needs and could be potentially hazardous as it is related to fatal complications such as aspiration pneumonia and severe malnutrition [321].

Interventions for neurogenic dysphagia are mainly based on functional swallowing therapy, including methods of restitution, compensation and adaptation. The aims of the interventions are to help patients maintain their nutritional status and most importantly to prevent aspiration and aspiration pneumonia [322]. Data regarding the effectiveness of behavioral, rheological and rehabilitation treatments for OD in patients with MS are limited. Studies evaluating the efficacy of interventions in MS patients either include a very small sample size of patients or are pilot studies, limiting their significance for formulating safe recommendations regarding the efficacy of interventions for the management of dysphagia in MS patients. Nonetheless, in patients with neurodegenerative diseases and dysphagia of neurological etiology, training in swallowing with triggering of reflexes, training of swallowing process and adjustment in the consistency of the food and liquids can help to improve the process of swallowing, help maintain sufficient nutritional intake and reduce the risk of aspiration [295,323].

Data regarding the effectiveness of thickened fluids or modified consistency foods are very scarce in MS patients, based not on randomized trials but on quantified examinations of the swallowing ability with or without the use of thickeners or different types of consistencies of food items [226,227]. Nonetheless, the use of thickened fluids is a common strategy to improve swallowing safety in a variety of opharyngeal dysphagic patients, including those who cannot sufficiently control the swallowing of thin liquids or when airway protection is disturbed during swallowing [324,325].

PEG is one of the most commonly used methods for enteral nutrition in patients who are unable to take food orally [326,327]. The most common indication is neurogenic dysphagia, followed by obstructive causes such as head and neck tumors. PEG is the route of choice for enteral nutrition in chronic neurological patients unable to feed themselves safely orally, as it is well tolerated and can lead to a significant improvement of nutritional status [328]. See supplementary data for Clinical Question 30.

6. Stroke

Stroke is one of the most prevalent acute neurological diseases and one of the world’s leading causes of mortality and physical disability in adults. The risk of stroke increases with age. Other identified known risk factors for stroke are hypertension, cigarette smoking, heart disease, diabetes, transient ischemic attacks, lack of exercise, alcohol, diet and obesity. According to the World Health Organization, the number of stroke events in EU countries, Iceland, Norway, and Switzerland is likely to increase from 1.1 million per year in 2020 to more than 1.5 million per year in 2025, solely because of the demographic changes [329]. Currently 6 million subjects live in these countries having survived a stroke. Approximately one-third of individuals who recover from their first stroke will have another stroke within 5 years. Recurrent stroke is a major contributor to disability and death. The global cost of stroke in Europe is estimated as high as 64 billion Euros [330].

Stroke patients are prone to malnutrition and dehydration mainly due to dysphagia, impaired consciousness, perception deficits and cognitive dysfunction. Being malnourished or at risk of malnutrition on admission is associated with an increased risk of mortality and poor outcome [331]. Furthermore, nutritional status can worsen during the first week after a stroke [332,333]. Stroke patients are also at high risk for aspiration pneumonia, a life-threatening complication with very high mortality. Early
detection and treatment of dysphagia would be a cornerstone in the management of stroke patients in order to decrease the incidence of malnutrition, dehydration and aspiration pneumonia. Several clinical questions arise about medical nutrition therapy in patients who have had a stroke.

6.1. Clinical Question 31: Which stroke patients should be screened and assessed for dysphagia?

**Recommendation 52:**

A formalized screening for dysphagia should be performed in all stroke patients as early as possible and before oral intake.

**Grade of recommendation B — strong consensus (95% agreement)**

**Recommendation 53:**

All stroke patients failing the dysphagia screening or demonstrating symptoms of or risk factors for dysphagia should be evaluated with a more thorough assessment of swallowing function as early as possible.

**Grade of recommendation B — strong consensus (100% agreement)**

**Commentary:**

Dysphagia affects at least 50% of patients with ischemic or hemorrhagic stroke [4,5]. In the acute stage of stroke aspiration pneumonia is the most important complication of dysphagia. Adjusted for other risk factors dysphagia more than doubles the risk for this complication [3]. Pneumonia in turn is associated with increased mortality, length of hospital stay, dependency at discharge and institutionalization [334,335]. Several studies have demonstrated that a formalized dysphagia screening and assessment is capable to reduce the rate of pneumonia [18,336–346]. In particular, the prospective registry-based cohort study by Bray et al. has demonstrated in 63,650 stroke patients that any delay in dysphagia screening and comprehensive dysphagia assessment leads to an increase in stroke-associated pneumonia in a strong time-dependent manner [347]. Therefore, screening and if necessary assessment for dysphagia should be performed as early as possible. The diagnostic approach starts with a formal aspiration screening, which may be a water swallow test [348–350] or a multi-consistency-test [351–354].

If a patient fails the screening or demonstrates signs of dysphagia, such as coughing, choking, wet voice, food-residuals in the mouth or pneumonia outside the screening test, a more thorough assessment has to be performed [350,355]. The same is true if the screening is negative, but risk factors for dysphagia such as dysarthria, aphasia, facial palsy, cognitive impairment, decreased level of consciousness and high stroke severity are present [349,355–359]. The more severe the stroke, the higher is the probability of dysphagia. In fact a National Institute of Health stroke scale of 10 and above demonstrated a high sensitivity and specificity in predicting dysphagia [360,361].

When it comes to a more comprehensive assessment, a clinical bedside assessment (CBA) performed by a speech and language therapist, a VFS or a FEES can be performed. Since the diagnostic properties of the CBA have been less well explored and questioned recently, instrumental testing should be preferred [179]. As a bedside method, FEES includes several advantages and needs only minimal cooperation of the patient. Therefore, it is predestined to be utilized as an assessment method in stroke patients. A study by Bax et al. could suggest that access to FEES was associated with a significantly reduced rate of pneumonia after stroke [339]. See supplementary data for Clinical Question 31.

6.2. Clinical Question 32: Does a routine screening of nutritional risk compared with standard care lead to lower morbidity and mortality or improve other outcomes in acute stroke patients?

**Recommendation 54:**

The available evidence suggests that all stroke patients should be screened for risk of malnutrition on admission to hospital (within 48 h), and the MUST can be used to identify patients who are more likely to benefit from medical nutrition therapy.

**Grade of recommendation: GPP — strong consensus (100% agreement)**

**Commentary:**

When compared to a normal nutritional status, malnutrition is associated with a worsened outcome in terms of increased mortality, length of hospital stay and hospitalization costs. The association between nutritional status and mortality was analyzed in a large cohort of 3012 patients with a recent stroke enrolled in the Feed Or Ordinary Food (FOOD) trial [332]. The 6-month mortality was higher in the group of 275 patients deemed malnourished, using a variety and often non-validated criteria, than in patients with normal nutritional status (37 vs 20%). These findings were confirmed recently using a formal nutritional screening tool in 543 patients with acute stroke. Using the Malnutrition Universal Screening Tool (MUST) to evaluate the risk of malnutrition within 48 h post stroke, from low to high, the authors found a 6-month mortality rate increasing from 6 to 42% [331]. Likewise, in this study, the length of hospital stay (LOS) and related costs increased as the risk of malnutrition rose from low to high. In fact, risk of malnutrition was able to predict the 6-month mortality, LOS and costs (related to the first and recurrent hospital admissions during the follow-up period) independently of age, gender, ethnicity, type of stroke, stroke severity and several stroke risk factors. This was the first study that validated a nutrition screening tool in the stroke population and its predictive validity suggests that MUST is a tool that can be used on stroke patients to identify those who are more likely to benefit from medical nutrition therapy. In two other recent studies, pre-stroke underweight or weight loss were associated with increased 30-d post-stroke mortality [362,363].

A few studies have failed to clearly demonstrate clinical beneficial effects of medical nutrition therapy in stroke patients [21]. This may be explained by the fact that many of those studies have not used nutrition screening or assessment tools validated for the stroke population, therefore they may have missed those who were more likely to benefit from nutritional therapy. See supplementary data for Clinical Question 32.

6.3. Clinical Question 33: Does individual dietetic counseling compared to standard care lead to lower morbidity and mortality or improve other outcomes in acute stroke patients with nutritional risk?

**Recommendation 55:**

Patients who are malnourished or at risk of malnutrition should receive medical nutrition therapy through an individual nutrition care plan. Whenever possible, a nutrition specialist should develop and monitor this plan.

**Grade of recommendation: B — strong consensus (91% agreement)**
handgrip strength (2.3 (SD 3.7) versus 2.0 (SD 4.9) kg; P = 0.055) and handgrip strength (2.3 (SD 3.7) versus −0.3 (SD 4.9) kg; P = 0.002), and some domains of the quality of life questionnaire (i.e. mobility, self-care and usual activities domains) although one quarter of these questionnaires were incomplete. There was no difference in length of hospital stay between groups.

Another two papers from the same author and using the same cohort of patients were found [365,366]. In the study that analyzed the body composition of this cohort of patients [365], the group that received the individualized nutritional treatment plan suffered less from unintentional weight loss in the first week of hospitalization, and the intervention subgroup of women had a smaller loss of body fat at 3 months, when compared with the control subgroup of women. The long term mortality (5−7 years post stroke) for this cohort was later analyzed [366] and resulted showed no statistically significant difference in this outcome between both groups. It should be noted that the nutritional intervention was delivered for a relatively short period of time (i.e. only during hospitalization, and advice to prevent malnutrition was given prior to discharge), therefore it remains unclear whether the long-term outcomes would have been influenced by a longer period of medical nutrition therapy. Larger and good quality RCTs, providing medical nutrition therapy for a longer period of time to patients identified at risk of malnutrition using a validated nutrition screening tool, will help to fill this gap in the evidence.

In summary, the existing evidence suggests that medical nutrition therapy, given through an individualized nutritional treatment plan tailored to the specific needs of the patient, can help to meet energy requirements and prevent weight and fat loss, and can also contribute to improvement of functional status and quality of life. Stroke patients are particularly vulnerable to malnutrition, and this is a complex problem that may require multiple strategies to ensure that the nutritional needs of the patients are met; to prevent further catabolism and to maximize the potential for rehabilitation. A nutrition specialist (e.g. a dietician or a nutritionist with experience in stroke) gathers the skills required to understand the multiple causes of malnutrition or the factors that place the patient at risk of malnutrition, and is well positioned within the multidisciplinary team to develop and monitor a nutrition care plan tailored to the specific needs of the patient. Therefore, it is recommended that, whenever possible, a nutrition specialist should develop and monitor the individual nutrition care plan. See supplementary data for Clinical Question 33.

6.4. Clinical Question 34: Do oral nutritional supplements compared to standard care lead to lower morbidity and mortality or improve other outcomes in acute stroke patients with nutritional risk?

**Recommendation 56:**

Routine ONS are not recommended for patients with an acute stroke without dysphagia and who are adequately nourished on admission.

**Degree of recommendation:** GPP — strong consensus (100% agreement)

**Recommendation 57:**

In stroke patients who are able to eat and who have been identified to be malnourished or at risk of malnutrition ONS are recommended.

**Degree of recommendation:** GPP — strong consensus (100% agreement)

**Commentary:**

In the acute phase of stroke, 30−50% of patients suffer from dysphagia, while the incidence drops to around 10% at six months of acute stroke. Dysphagic stroke patients are prone to dehydration and malnutrition, and also have an increased risk of aspiration pneumonia and global mortality. The relevance of an early detection of malnutrition and dysphagia is well defined, but there are few studies on the effect of ONS in stroke patients who are able to eat and who have been identified as malnourished or at risk of malnutrition [19−21]. In the overall group of stroke patients without dysphagia, ONS do not improve survival or functional outcome, and only some positive results have been demonstrated in patients clearly identified as malnourished. There are very few studies focusing on this topic in the literature.

Gariballa [367] and Rabadi [368] evaluated the effect of providing ONS to stroke patients identified as malnourished or at risk of malnutrition on mortality, dietary intake, body weight, functional status, length of hospital stay and the proportion of patients discharged home. Gariballa [367] in a small trial (20 patients per arm) explored the effect of ONS (400 ml/d, 1.5 kcal/ml and 5 g protein/100 ml) in addition to normal hospital diet, compared to normal hospital diet alone for 4 weeks. Significant differences were found at 12 weeks only for energy and protein intake, serum iron and albumin, with no differences in any other outcomes (e.g. Barthel-Index, infectious complications, length of stay and mortality). Rabadi [368], in a trial including 58 stroke rehabilitation patients per arm, compared the effect of a high-energy high-protein ONS (2 kcal/ml, 9 g protein/100 ml) with a standard energy and protein ONS (1 kcal/ml, 4 g protein/100 ml) on length of hospital stay, functional outcomes, timed walking test and body weight. The group on high-energy high-protein ONS showed better outcome measures as functional independence measure motor score and 6-min walking test, but not in functional independence measures cognition score, length of hospital stay or body weight.
The largest trial (FOOD trial, Food or Ordinary Diet after Stroke) [369] included 4023 patients and evaluated the effects of routine provision of ONS (360 ml/d, 1.5 kcal/ml, 6 g protein/100 ml) in addition to hospital normal diet (irrespective of nutritional status) with normal diet alone on hospital length of stay, mortality, poor outcome (death or dependency), in-hospital complications, discharge destination, quality of life and adverse events. In this trial, there were no statistically significant differences between the groups in any of the outcomes measured. However, there were several limitations in the study design that might explain this lack of effect. The most important was that nutritional assessment was not standardized, and then it was difficult to assess the influence of a nutritional intervention on nutritional status. The second limitation was the lack of monitoring of energy intake during the intervention period or at follow-up, and then it was difficult to assess whether the intervention group achieved a higher nutritional intake than the control group.

As mentioned above (question 33) Ha et al. [364] evaluated the effect of an individualized nutrition treatment plan including ONS or enteral feeding as required, compared with usual care in acute stroke patients aged > 65 years identified as malnourished or at risk of malnutrition (MUST) on energy and protein intake, body weight, quality of life, handgrip strength and length of hospital stay. This intervention group showed higher energy intake, prevention of weight loss, improved quality of life and handgrip strength at 3 months, but no significant differences were found on protein intake and length of stay. Unfortunately, in this study the effect of ONS or tube feeding could not be differentiated. Recently, the group has published a survival study after 5–7 years of follow-up [366], and no differences were found in survival between the control and the intervention group, with the exception of the subgroup of patients who had baseline plasma total carotenoids above median levels, that increased all-cause mortality. See supplementary data for Clinical Question 34.

6.5. Clinical Question 35: Does offering texture modified food compared to standard nutrition lead to lower morbidity and mortality or improve other outcomes in acute stroke patients with dysphagia?

Recommendation 58:

Texture modified diets and thickened liquids may reduce the incidence of aspiration pneumonia in stroke patients with dysphagia. Data on the effect of modified diets and thickened liquids on mortality of stroke patients is insufficient.

Texture modified diets and thickened liquids should be ordered only following an assessment of swallowing function including assessment of the risk of aspiration according to a standardized protocol (clinical and, if feasible, instrumental) by professionals trained and experienced in the assessment and treatment of dysphagia. This assessment should be repeated at regular intervals until normal swallowing function is regained.

Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 59:

Every stroke patient who receives texture modified diets or thickened fluids should be referred for specialist nutritional assessment and counseling. This assessment should be repeated at regular intervals at least for as long as texture modification and/or thickened fluids are continued.

Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 60:

Texture modified diets and thickened liquids may lead to reduced energy and fluid intake.

Every stroke patient who receives texture modified diets or thickened fluids should have both fluid balance and nutritional intake monitored by trained professionals.

Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 61:

In stroke patients diagnosed with thin liquid aspiration free access to water in addition to thickened liquids may be an option to thickened liquids alone.

Stroke patients diagnosed with risk of thin liquid aspiration may be allowed unthickened water in addition to thin liquids on an individual decision with regular follow-up.

Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 62:

Carbonated liquids may reduce pharyngeal residue when compared to thickened liquids. The use of carbonated liquids may be an option for stroke patients diagnosed with pharyngeal residue.

Grade of recommendation: GPP – strong consensus (100% agreement)

Commentary:

Texture modified food and thickened liquids are usually used in patients with dysphagia to reduce the risk of choking and aspiration. Foods are chopped, mashed or pureed to compensate for chewing difficulties or fatigue, improve swallowing safety and avoid asphyxiation. Liquids are typically thickened to slow their speed of transit through the oral and pharyngeal phases of swallowing, to avoid aspiration of material into the airway and improve transit to the esophagus. Although these interventions are well established and frequently used in clinical practice, randomized controlled trials with texture modified food and thickened liquids are rare. In clinical practice fluids are thickened using subjective judgement. Most studies combined interventions with texture modified food and thickened liquids making it difficult to separate which of the two combined interventions was the one which was effective. The names, the number of levels of modification and characteristics of text modification, e.g. “thin”, “nectar-like”, “honey-like”, “spoon-thick”, “pudding” vary within and across countries [370]. Due to this lack of an international terminology for texture modified foods and thickened liquids, it is not possible to compare clinical trials with this intervention. Furthermore, it is difficult to transfer results from studies where the intervention-texture modification-is not standardized. A great contribution to oral fluid intake is from food [371].

A systematic review of randomized controlled trials [372] on dysphagia treatment post stroke identified and reviewed the following 4 trials with interventions based on dietary modifications. In a RCT including 56 patients with pseudobulbar dysphagia, the effect of bolus manipulation on the recurrence of aspiration pneumonia was studied. Group I patients received a “pureed diet” with thin liquids, whereas those in group II received a “soft mechanical diet” with thickened liquids. Members of group II experienced significantly fewer incidences of aspiration pneumonia during a 6-month period [373].
A small randomized-controlled prospective trial included 20 stroke patients with previously identified thin liquid aspiration. The control group (10 patients) received thickened liquids only. The study group (10 patients) had all liquids thickened in the same manner, but were allowed free access to water between meals in addition to the thickened liquids. No patient in either group developed pneumonia, dehydration, or complications during the course of the study, or during 30-day follow-up period. Control group subjects (thickened liquids only) averaged a mean of 27.2 days in the study (range 8–64 days) prior to reaching the end point of no thin liquid aspiration as documented by follow-up videofluoroscopic evaluation. Control group subjects had a mean intake of 1210 cc/day (range 400 to 1800 cc/day) of thickened liquids. Study group subjects averaged 32.9 days from onset of stroke to end point of no thin liquid aspiration, with a mean of 19.1 days in the study (range 7–35 days) prior to reaching the end point of no thin liquid aspiration as documented by follow-up videofluoroscopic evaluation. The mean water intake was of 855 cc/day (range 200–800 cc/day). It has to be stressed that patients in the study group had only additional access to water—not to other liquids like juice which pose an additional risk if aspirated due to the content of acid. Furthermore, the compliance was not assessed. In clinical practice many patients who are offered thickened liquids take additional fluids without thicker [374].

In one study included in the systematic review of Foley et al. [372], both groups received thickened fluids. This means the study did not evaluate the effect of thickened liquids compared to unthickened liquids but the effect on monitoring the fluid thickness using a viscometer. The speech and language therapist determined the optimal fluid thickness for each patient. The prescribed fluid viscosity for the intervention group was obtained using a viscometer. Patients in the control group received fluids prepared according to current practice, i.e. the amount of thicker required to produce the prescribed viscosity was judged subjectively by the nursing staff. Ten patients in the study group (n = 23) and nine in the control group (n = 23) aspirated. The mean viscosity of fluids offered to patients in the control group was significantly higher than that of the study patients. There was a statistically significant correlation between the viscosity and the residual volume of fluid (Pearson’s test: r = 0.7, p < 0.02). The findings of the study suggest that fluids prepared by subjectively assessing the amount of thicker required to produce a given consistency tend to have a higher viscosity than those prepared using the viscometer. However, the higher viscosity does not appear to protect against pulmonary aspiration and may lead to a reduced fluid intake [375].

Another study included in the systematic review of Foley et al. [372], compared starch-based powder-thickened fluids with ready prepared pre-thickened fluids in 24 patients with dysphagic acute stroke requiring thickened fluids. Patients who were not on specialist stroke units and received pre-thickened fluids drank almost 100% more than those on powder-thickened fluids (p = 0.04) [376].

A RCT with patients with known thin liquid aspiration post stroke randomized stroke patients in rehabilitation facilities to receiving “thickened liquids only” or a “water” protocol. For the 14 participants in rehabilitation facilities whose data proceeded to analysis, there was no difference in the total amount of beverages consumed between the water protocol group (mean = 1103 ml per day, SD = 215 ml) and the thickened liquids only group (mean = 1103 ml SD = 247 ml). Participants in the water protocol group drank on average 299 ml (SD 274) of water but offset this by drinking less of the thickened liquids. Their hydration improved over time compared with participants in the thickened liquids only group, but differences between groups were not significant. Twenty-one percent of the total sample was diagnosed with dehydration, and no participants in either group were diagnosed with pneumonia. There were significantly more diagnoses of urinary tract infection in the thickened liquids only group compared to the water protocol group (χ2 [2] = 5.091, p = 0.024), but no differences between groups with regard to diagnoses of dehydration (χ2 [2] = 0.884, p = 0.347) or constipation (χ2 [2] = 0.117, p = 0.733) [377].

According to a literature review, the impact of bolus modification on health-related quality of life in patients with oropharyngeal dysphagia appears to be negative with increased modification of food and fluids often correlating with a decreased quality of life [378]. For this reason, adequate texture modified diets and thickened fluids may be supportive in selected patients with oropharyngeal dysphagia, however, may lead to decreased quality of life in others. Dietary and fluid intakes of older adults in care homes requiring a texture modified diet are significantly less than individuals on a standard texture diet. Residents on a texture-modified diet had significantly lower intakes of energy (1312 kcal versus 1569 kcal) (P < 0.04), non-starch polysaccharide (6.3 [1.7] g versus 8.3 [2.7] g, P < 0.02) and fluid (1196 ml versus 1611 [362] ml, P < 0.002) when compared with residents on a standard texture diet [379].

In one study observing the intake of people eating normal diet compared to people eating texture modified food, the texture modified group had significantly lower intakes of energy (3877 versus 6115 kcal/day, P < 0.0001) and protein (40 versus 60 g/day, P < 0.0003) compared to consumption of the normal diet. The energy and protein deficit from estimated requirements over 24 h was significantly greater in the texture modified group (2549 versus 357 kcal, P < 0.0001; 6 versus 22 g, P = 0.013; respectively) [380].

In a study including thirty-nine patients with a new diagnosis of ischemic stroke patients were assigned to one of two groups based on the consistency of liquids. Group 1 (n = 21), thin liquids, and group 2 (n = 18) received nectar or honey consistency. Fluids offered and consumed were monitored for 72 consecutive hours. Patients receiving thin liquids consumed significantly more than patients receiving thickened liquids (mean = 1405.45 ml and SD = ±727.1 ml vs. mean = 906.58 ml and SD = ±317.4 ml; p = 0.0031). However, they were also offered significantly more fluids (mean = 2574.7 ml vs. 1588.9 ml, p = 0.0002) [381].

In a retrospective chart review completed on 67 ischemic stroke patients, patients on modified solid diets or thickened liquids due to dysphagia showed a significantly elevated BUN/Cr values at discharge [382], as a indicator of poor hydration status.

In a small study neurologically impaired patients had to swallow liquids with the following consistencies three times: thin, thickened and carbonated. The liquids were given in doses of 3 × 5 ml. The swallows were analyzed videoradiographically regarding penetration/aspiration, pharyngeal transit time and pharyngeal residue. Significant difference was found regarding penetration/aspiration when comparisons were made between thin liquid and carbonated thin liquid (p < 0.0001). The comparison between thin liquid and thickened liquid (p < 0.0001) showed significant less penetration with thickened liquids. Pharyngeal residue was significantly reduced (p < 0.0001) with carbonated thin liquid compared to thickened liquid. Pharyngeal transit time was reduced both when comparing thin liquid with thin carbonated liquid (p < 0.0001) and thickened liquid (p < 0.0001). However, this study did only look at swallowing during a videoradiographic analysis, not on swallowing outside laboratory conditions and did not investigate clinical endpoints like aspiration pneumonia [383].

In summary, currently there is a lack of evidence on the positive as well as on the adverse effects of texture modified diets in stroke patients with dysphagia. Many trials with texture modified food
and thickened liquids as an intervention do not focus especially on stroke patients. See supplementary data for Clinical Question 35.

6.6. Clinical Question 36: Does tube feeding compared to other feeding strategies lead to lower morbidity and mortality or improve other outcomes in acute stroke patients with severe dysphagia?

**Recommendation 63:**

Patients with prolonged severe dysphagia after stroke that presumably last for more than 7 days should receive early (not more than 72 h) enteral tube feeding.

Grade of recommendation: GPP — strong consensus (100% agreement)

**Recommendation 64:**

Critically ill stroke patients with decreased level of consciousness that need mechanical ventilation should receive early (not more than 72 h) enteral tube feeding.

Grade of recommendation: B — strong consensus (100%)

**Commentary:**

Around 8.5—29% of stroke patients require tube feeding in the acute phase of stroke [384]. However, it remains unclear what kind of stroke patients can improve their prognosis with enteral feeding [19—21]. Probably, previously malnourished patients could benefit the more, although this affirmation has not been proved. In the FOOD trial-2 [385], early enteral feeding (within seven days after stroke) was compared with tube feeding initiated after seven days in 859 patients. Early tube feeding reduced mortality in dysphagic patients by 5.8%, compared with the group of “late” initiation, although the differences were not significant. However, the proportion of patients surviving with poor outcome (great disabilities) was higher in the group who started early enteral nutrition, as well as prevalence of gastrointestinal bleeding. It could be speculated that these patients with poor outcome probably would not have survived without enteral nutrition. This study suffers from important limitations in the design. The first is the lack of standardization of nutritional assessment (as previously stated), but probably the most important bias for this question is that patients with a clear indication for early tube feeding were not included, only those in which the attending physician was unsure about the adequate nutritional therapy. Zheng [386] evaluated the impact of early enteral nutrition (within 72 h of admission) on short term prognosis after acute stroke. However, this non-randomized study has serious limitations in the design, as they compared 75 patients admitted to a stroke unit managed with enteral nutrition with 71 patients admitted to the regular ward that received family-managed oral nutrition.

Critically ill stroke patients with a severe decreased level of consciousness that need mechanical ventilation can benefit from enteral nutrition. In ESPEN Guidelines on enteral nutrition: Intensive care [387], critically ill patients benefit from early medical nutrition therapy (preferably by the enteral route) if they cannot meet their nutritional requirements by the oral route within three days. Although the studies that support this recommendation are not performed specifically in stroke patients, the beneficial effects may be extrapolated to stroke patients.

Patients with presumably long duration of dysphagia (more than 7 days) because of the severity of stroke or certain cerebral infarct localizations (as bulbar and brainstem areas) are at nutritional risk and therefore they can benefit from enteral nutrition. In these cases, enteral nutrition should start early, as acquired malnutrition is a negative prognostic factor for outcome in stroke patients [333,388,389]. See supplementary data for Clinical Question 36.

6.7. Clinical Question 37: Does tube feeding via PEG compared to nasogastric tube feeding lead to lower morbidity and mortality or improve other outcomes in acute stroke patients with dysphagia?

**Recommendation 65:**

If a sufficient oral food intake is not possible during the acute phase of stroke, enteral nutrition should be preferably given via a nasogastric tube.

Grade of recommendation: A — strong consensus (100% agreement)

**Recommendation 66:**

If enteral feeding is likely necessary for a longer period of time (>28 days), a PEG should be chosen and placed in a stable clinical phase (after 14—28 days).

Grade of recommendation: A — strong consensus (95% agreement)

**Recommendation 67:**

In a subgroup analysis of patients with dysphagia needing PEG placement, the “pull” technique was superior and then should be preferred when compared with the “push” technique.

Grade of recommendation: B — strong consensus (100% agreement)

**Recommendation 68:**

Stroke patients mechanically ventilated for longer than 48 h may receive a PEG at an early stage (usually within 1 week).

Grade of recommendation: 0 — consensus (85% agreement)

**Recommendation 69:**

If a nasogastric tube is repeatedly removed accidentally by the patient and if enteral nutrition will probably be necessary for more than 14 days, a nasal loop/bridle may be applied to secure the nasogastric tube.

Grade of recommendation: B — strong consensus (95% agreement)

**Recommendation 70:**

If a nasogastric tube is rejected or not tolerated (after several attempts) by the patient and if medical nutrition will probably be necessary for more than 14 days and the application of a nasal bridge is not feasible or not tolerated, early feeding via PEG should be started.

Grade of recommendation: B — strong consensus (93% agreement)

**Recommendation 71:**

Nasogastric tube feeding does not worsen dysphagia and is therefore no obstacle to dysphagia rehabilitation.

Dysphagia therapy should therefore start as early as possible in all stroke patients.

Grade of recommendation: B — strong consensus (90% agreement)
Recommendation 72:

If there are symptoms of unexplained worsening of dysphagia in patients fed via nasogastric tube, the pharyngeal tube position should be controlled endoscopically.

Grade of recommendation: GPP – strong consensus (90% agreement)

Commentary:

Between 23 and 78% of all stroke patients suffer from relevant dysphagia, dependent on the diagnostic technique [4,390]. Frequently, this leads to aspiration within the first days after stroke. The majority of patients have “silent” aspiration [391]. Severity of stroke, aphasia, as well as dysphagia, and lesions of the frontal and insular cortex as well as the brain stem are predictors for prolonged dysphagia (>14 days) [4,384]. Between 8.5% and 29% of stroke patients require tube feeding in the acute phase of stroke [392].

Dysphagia due to ischemic stroke resolves within 7–14 days in 73–86% of the cases [393–395]. It is therefore worthwhile to consider an access to enteral nutrition which is less invasive than PEG at first. At present, only two prospective, randomized, controlled intervention studies had been comparing nasogastric tube feeding and PEG feeding after stroke.

In a recent Cochrane review, feeding of adults with swallowing disturbances via PEG tube versus feeding via nasogastric tube were compared [396]. However, the population included adults with swallowing difficulties of various etiologies, i.e. also patients with dysphagia caused by other diseases than by stroke were included. Intervention failure occurred in lower proportion of participants with PEG compared to nasogastric tubes. There was no statistically significant difference of the secondary outcomes mortality, overall reports of adverse events at any follow up time point, specific adverse events including pneumonia and nutritional status. However, there was evidence in favor of PEG of mid-arm circumference change from baseline and levels of serum albumin were higher in the PEG group. Quality of life was measured in two studies with 133 participants. The intervention favored PEG: Fewer patients found the application of a PEG to be inconvenient, uncomfortable or interfering with social activities. The studies were subgrouped by endoscopic technique into pull, push and “not reported”. There was a significant difference favoring the “pull” subgroup. The most widely used method of PEG placement is the “pull” method or standard Ponsky technique. The “push” modification of this procedure, based on the Russell introducer technique, avoids transoral passage of the PEG by direct insertion through the abdominal wall over a guidewire under endoscopic guidance. As this Cochrane review did not specifically address stroke patients with dysphagia, we analyzed studies especially addressing this patient group.

In a Cochrane review on “Interventions for dysphagia and medical nutrition therapy in acute and subacute stroke” [21] the authors conclude that, compared with nasogastric feeding, PEG reduced treatment failures and gastrointestinal bleeding and had higher feed delivery. Albumin concentrations were higher in the PEG group. The study published by Norton et al. [397] included 30 stroke patients. 16 patients were assigned to the PEG-group. They had a better nutritional status, lower mortality and shorter hospital stay after 6 weeks of intervention. However, it has to be taken into account that the study population consisted of severely impaired elderly stroke patients, with an average age of 79 years. All patients were unconscious on admission, had hemiplegia and their Barthel-Index (Katz Index for Activities of Daily Living, ADLs) was only three points on average (on a scale from 0 to 20 points).

The only randomized, controlled study evaluating timing of feeding in stroke patients, was the “Early versus Avoid Trial” of the FOOD-study, which was published in 2005 [369,398]. It was also the study with the biggest sample size (859 patients) addressing this question. After randomization tube feeding was either started as soon as possible or the placement of the tube was delayed for at least seven days. During this period, fluid was given intravenously or subcutaneously. Whether enteral nutrition was given via a PEG-tube or a nasogastric tube, was decided by the attending physician. In 429 patients, a nasogastric tube was chosen; only 10 patients received a PEG-tube. The group of patients that started enteral nutrition within 7 days of admission had a reduction in mortality by 5.8%, which was not significant. The proportion of patients surviving with poor outcome was greater in the group with early nutrition (defined as Rankin Score 4 or 5). It could be speculated that these patients with an “impaired outcome” would have died with a delayed start of nutrition. Pneumonia did not occur more often in patients that received early enteral nutrition. Gastrointestinal bleeding occurred more often in early feeding than in delayed feeding. In this study, patients were only included when the attending physician was not sure about the timing of feeding. Nutritional status was not evaluated by standardized screening, but recorded informally by the attending physician. Together with some other limitations of the study, the amount of tube feed given was not documented completely.

It is recommended to start early enteral nutrition in patients, who are anticipated to have swallowing difficulties for more than seven days and therefore not reach a sufficient oral intake. The FOOD-trial showed no differences between PEG feeding and nasogastric tube feeding regarding the endpoint “death after six months” in 321 dysphagic stroke patients [369,398]. The mean age of the study population was 76 years. At admission 16% of patients could raise both arms, 3% could walk without help and 25% had a normal verbal Glasgow Coma Scale. After six months patients with nasogastric tube showed a significantly (7.8%) lower risk of the combined end point “death and/or impaired functional status” when compared to patients with early PEG feeding. A limiting factor of the study was that only patients, in whom the attending physician was “not sure” about the best nutritional therapy (which means nasogastric or PEG tube), were included. Unfortunately, this study does not give information about the number of patients per center that were not included in the study and the reasons for exclusion. Furthermore, tube placement occurred considerably later in patients, who were randomized to the PEG-group than in patients in the nasogastric-group. Eighty percent of the patients with the nasogastric tube received tube on the first day after randomization. In the PEG-group only 70% of PEG-tubes were placed within 4 days, 80% were placed within 14 days after insult. In this study, most patients were recruited in British hospitals, where, at the time of the study, it took several days to get an appointment for PEG-tube placement. The fact that intervention was not possible directly after randomization, limits the comparability between the two study groups. The effects of a delayed nutrition therapy are known from other studies, amongst others from the “Avoid versus Early-tube”-part of the FOOD-trial. There was an increased prevalence of pressure sores in the PEG-group. Two possible explanations of the difference can be discussed: On the one hand patients with a PEG-tube might have been less mobile, due to the tube placed in the abdominal region and therefore suffered from an increased rate of pressure sores. On the other hand, it is conceivable, that patients with a PEG were attended differently (e.g. less intensively) by the nursing staff than those with a nasogastric tube. In case of the latter theory, the worse functional result of the PEG-group would not have been directly caused by the enteral access and nutrition, but by the different treatment and care of the patients. Taking into account the inclusion criteria, the results of the FOOD-trial have to be treated with
caution when applied to the overall group of dysphagic stroke patients.

In another small prospective randomized study published by Park et al. [399], a group of 40 patients with persisting neurological dysphagia – 18 were stroke patients, the patients fed via PEG tube had a better nutritional status compared to the group fed via nasogastric tube. On day twenty-eight 18 out of 19 patients in the nasogastric tube—group had fulfilled the criteria for a “treatment failure”: hereupon feeding was changed to PEG-tube. Outcome could not be evaluated due to the small number of patients left in the nasogastric group. This is showing the common practical problems with a nasogastric tube, like non-tolerance of the nasogastric tube.

In general, dislodgement of nasogastric tubes causing poor enteral nutrition is a common problem in daily routine. Two studies about nasal loops in stroke patients demonstrated that nasal loops are safe, well tolerated and effective at delivering full enteral nutrition [400]. A randomized controlled trial observed an increase of 17% mean volume of fluid and tube feed given in the nasal loop group. The intervention period was limited to 2 weeks. The nasal loop ameliorated electrolyte disturbances and reduced nasogastric tube failure. However, no differences were seen in terms of mortality, morbidity, PEG placement, functional outcomes and length of hospital stay at 3 months follow up [401]. The long term outcome in this patient group was poor: 88/104 (84%) were either dead or severely disabled at 3 months follow up. There is insufficient evidence to support a recommendation of mittens. In centers where they are used, a locally agreed protocol should be in place to minimize the risk of associated complications [20].

A randomized study published by Kostadima et al. [402] reported that early nutrition (within 24 h) via PEG in 41 mechanically ventilated patients with stroke or head injury was superior to feeding via nasogastric tube, and it was associated with a lower prevalence of ventilator-associated pneumonia. However, a significant difference in length of stay and mortality could not be found. Conclusions for the treatment of ventilated stroke patients can be drawn from this study, as stroke patients were represented with 61%. In particular, in mechanically ventilated stroke patients, in whom prolonged artificial nutrition (>14 days) is probable, early feeding via PEG (usually within 1 week) should be preferred to nasogastric tube feeding, due to a lower rate of ventilation related pneumonia [402,403].

Particularly in stroke patients with unfavorable prognosis, ethical considerations and living-will decisions should be specially considered. In doubt, a semi-invasive nutrition with nasogastric tube feeding might be more appropriate as a first step. The indication for artificial nutrition should be reconsidered daily and in particular thoroughly reassessed before transfer to a nursing home or a palliative-care unit. Tube feeding may be finished, if the medical indication no longer exists, most likely in a palliative situation. In patients with an uncertain prognosis, PEG-insertion should not be a criterion for the admittance to a rehabilitation ward or to a nursing home, especially if a nasogastric tube is well tolerated.

Due to the risk of internal pressure sores, small diameter nasogastric feeding tubes (8 French) should be used in stroke patients. Tubes with a greater diameter should only be placed if gastric decompression is necessary. The placement of a nasogastric tube should be done by trained and technically experienced medical staff. Due to the risk of misplacement, the correct position should be controlled before the application of tube feed. This can be done via x-ray or by the aspiration of gastric content. A further possibility to control tube position is the measurement of gastric pH [404]. A local standard for the assessment of correct tube placement should be developed in every hospital. In a group of patients with miscellaneous diseases swallowing difficulties were observed in 17.4% of patients with nasogastric tube feeding, compared to none in the PEG group [405]. In addition to another study, which observed alterations of swallowing in healthy volunteers [406], these results partly led to the assumption that therapy for dysphagia might not be possible with a nasogastric tube in situ. This assumption is contradicted by three recent studies, with two of them in stroke patients, that did not observe a negative impact of nasogastric tube feeding on swallowing function [407–409]. Dysphagia therapy should therefore start as early as possible, in tube-fed as well as non-tube-fed patients. Dziwas et al. demonstrated that in most cases of worsening of dysphagia with a nasogastric tube, this was due to misplacement with coiling of the tube in the pharynx [409]. A reinsertion of the tube or even more favorable an endoscopic evaluation of the pharyngeal tube position is therefore recommended in this situation.

7. Oropharyngeal dysphagia. Additional aspects

7.1. Clinical Question 38: What is the role of food texture and liquid viscosity modification in the treatment of oropharyngeal dysphagia?

Recommendation 73:

There is strong evidence that the risk of aspiration can be reduced in adults with oropharyngeal dysphagia of different etiologies by increasing liquid viscosity. However, thickened liquids may increase the risk of post-swallow oral and pharyngeal residues.

Recommendation 47:

Texture modified diets and/or thickened liquids should be prescribed only after a clinical swallow exam and/or instrumental dysphagia assessment (VFSS or FEES) has been carried out.

Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 48:

To improve patients’ compliance different types of thickening agents should be offered for choice.

Grade of recommendation: GPP – strong consensus (95% agreement)

Recommendation 49:

Modified textures and thickened liquids should be used in persons with chronic dysphagia to enhance nutritional status.

Grade of recommendation: B – strong consensus (100% agreement)

Recommendation 77:

In spite of applying food texture and liquid viscosity modifications patients with OD are at an increased risk of malnutrition, dehydration and aspiration pneumonia and, hence, should be carefully monitored for these complications.

Grade of recommendation: GPP – strong consensus (95% agreement)
Commentary:

The use of texture-modified foods and thickened liquids has become a cornerstone of clinical practice to address OD. The principle behind this approach arises from the assumption that modifying the properties of normal foods and liquids will make them safer and easier to swallow [410]. In spite of the pervasive use of texture modifications as clinical intervention, the specific scientific foundation, although convincing in some aspects, is with regards to some important issues still incomplete or inconclusive.

For decades there were no established and universally used terminology and definitions to describe the target consistency recommended for patients with OD and to guide its preparation [410]. Several countries have developed their own taxonomies or classification systems [410,411]. Only recently the “International Dysphagia Diet Standardization Initiative” (IDDSI) has been established that pursues the goal to develop global standardized terminology and definitions for texture modified food and thickened liquids for individuals of all ages, in all care settings, and all cultures [412]. In general, an inconsistent approach in defining and measuring rheological properties of food and liquid items limits the comparability of studies performed and the validity of conclusions reached in this area. There is a strong need for establishing internationally accepted and uniformly used standards of measuring and grading rheological characteristics of bolus textures.

In spite of these problems with regards to terminology, the effect of liquid thickening on the physiology of impaired swallow responses has been thoroughly investigated. There are two recent systematic reviews [410,412] and one white paper [413] summarizing the evidence of more than thirty studies devoted to this topic. The concordant conclusion of these three high-quality papers is that liquid thickening reduces the risk of airway penetration and aspiration in different patient populations suffering from OD. Although the available data are insufficient to suggest particular viscosity values, the analysis put forward by Newman and colleagues suggest that on the continuum covering the whole spectrum from “thinn”, “nectar”, “honey” to “spoon thick” there seems to be a dose–response characteristic with thicker liquids being safer than thinner liquids [413]. On the other side of the same medal, liquid thickening seems to increase the risk of post-swallow residues [410,412,413]. Although not as unequivocal and as frequently studied as aspiration, several studies reported oral and/or pharyngeal residues with ultra-thick liquids [79,414–416].

Apart from these physiological effects, clinically relevant endpoints have also been studied in the context of liquid thickening and texture modifications. Contrasting with its positive effect on swallowing safety liquid thickening has failed to substantially improve fluid intake in several studies [375,376,417,418] and systematic reviews [202,419,420] with aversion for this type of diet being probably among the main reasons for this finding [421]. Thus, thickeners are suggested to suppress flavor, induce a “coating feeling” in the mouth and do not reduce the physiological sensation of thirst [422]. As a consequence of all these aspects, the use of thickeners has been associated with a decreased quality of life in a recent systematic review [378]. Interestingly, differences in the palatability of different thickeners, in particular starch-versus gum-based thickeners, have been identified at the individual level and with regards to the thickened beverages [423,424].

Apart from the viscosity, type of thickeners also impact on other characteristics of the liquids like texture, taste and appearance. There is evidence that the different types of thickening agents available differ in this respect, leading to differences in palatability and, potentially, in patients compliance.

The impact of feeding strategies involving texture modified diets on oral intake has been assessed in one small RCT [425]. In elderly dysphagic nursing home residents, both dietary intake and nutritional status significantly increased in the intervention group over a time period of 12 weeks. In addition, a cohort study in acute stroke patients showed that by being given a dysphagia diet patients could achieve more than 75% of their energy requirements [426].

The effect of dietary interventions in the prevention of aspiration pneumonia has been evaluated in several systematic reviews related to nursing home residents with dementia [427], elderly persons with stroke [372] and elderly persons with OD of heterogeneous etiologies [202,419,420]. It is generally concluded that the number of high quality studies is too low to recommend the use of texture modified food and thickened liquids for the prevention of aspiration pneumonia. In particular, Robbins et al. in their large RCT recruiting over 500 patients with OD due to Parkinson’s disease or dementia and proven aspiration on thin liquids, did not find a significant difference in the incidence of aspiration pneumonia between the group receiving thickened liquids and the group being treated with chin-down posture and normal liquids [227].

7.2. Clinical Question 39: Which exercises and maneuvers to rehabilitate oropharyngeal dysphagia are available?

Recommendation 78:

Prior to initiating a behavioral swallowing therapy patients should be assessed by a clinical swallowing exam or, preferentially, by an instrumental testing (VFSS, FEES). During the further course treatment effects should be reevaluated on a regular basis.

Grade of recommendation: GPP — strong consensus (95% agreement)

Recommendation 79:

There is strong evidence that the Shaker head lift, a combination of an isometric and an isokinetic exercise, has favorable long-term effects by improving the strength of the suprahyoid muscles over time, and increasing the opening of the upper esophageal sphincter. We recommend the Shaker head lift for the treatment of upper esophageal sphincter dysfunction.

Grade of recommendation: A — strong consensus (100% agreement)

Recommendation 80:

There is evidence that expiratory muscle strength training (EMST training) improves swallowing dysfunction in OD of different etiologies.

EMST is recommended in patients with motor-neuron disorders and Parkinson’s disease. EMST treatment should preferentially be applied within RCT.

Grade of recommendation: GPP — strong consensus (100% agreement)

Recommendation 81:

The chin-down maneuver is recommended in patients with premature spillage and predeglutitive aspiration.

Grade of recommendation: B — strong consensus (94% agreement)
**Recommendation 82:**

**Systematic and sufficiently frequent swallowing therapy making individualized use of the different exercises available is recommended in patients suffering from OD.**

**Grade of recommendation:** B — strong consensus (100% agreement)

**Commentary:**

Exercises and maneuvers probably constitute the most widespread treatment approach for patients with OD worldwide. A variety of different interventions exist, ranging from direct to indirect, isolated to combined and those incorporating swallowing and non-swallowing tasks. Rehabilitation exercises are intended to change and improve the swallowing physiology in force, speed or timing and are meant to produce long-term effects. In contrast to this, compensatory interventions are used for short-term effects on the swallow [428]. Contrasting with its wide-spread application, the scientific evidence for the efficacy of this type of treatment is heterogeneous with a general lack of large RCTs providing clinical meaningful endpoints [202,429].

The Shaker head lift is one of the best studied exercises used in dysphagia rehabilitation for many years and is designed for patients with weakness of the suprahypoid muscles and impaired opening of the upper esophageal sphincter [430]. This procedure is a head rising exercise with an isometric high-intensity portion with three head lifts held for 60 s with a 60 s rest period between each one and an isokinetic low-intensity portion that included 30 consecutive head lifts of constant velocity without holding. The Shaker head lift has been evaluated in systematic reviews [202,431] and several RCT [432-436] showing that this treatment improves strength and endurance of the suprahypoid muscles and upper esophageal sphincter opening. In addition, there is evidence that residues and aspiration events are reduced.

The chin-down is a technique used for patients who have decreased airway protection associated with delayed swallow initiation and/or reduced tongue base retraction. Patients are instructed to “bring their chin to their chest” and maintain this posture throughout the duration of the swallow [430]. In several studies, physiological changes like expansion of the vallecular recesses, approximation of the tongue base toward the pharyngeal wall, narrowing of the entrance to the laryngeal vestibule, expedited onset of laryngeal vestibule closure, reduction in distance between hyoid and larynx, and increased duration of swallowing apnea [430,437,438]. In two well-designed cohort studies of patients with OD presenting with aspiration, the aspiration risk could be reduced by approximately 50% [439,440].

Among the muscles that can be targeted by exercise are also those of the tongue, which plays a major role in bolus formation, control and propulsion in swallowing. Several studies show that tongue strength declines in healthy aging [441,442] and reduced tongue strength has been identified as a risk factor for aspiration [443,444]. Tongue strength training has been evaluated in OD in some well-done cohort studies [445-447]. These trials report different improvements of swallowing variables like vallecular residues and swallowing safety.

The Lee Silverman voice treatment has been designed to improve vocal intensity in PD patients. In one small cohort study of 8 PD patients the authors found several improvements in the oral and pharyngeal stage of swallowing [231]. There is insufficient evidence to recommend the Lee Silverman voice treatment to improve OD.

Respiratory muscle strength training (EMST) involves exhaling quickly and forcefully into a mouthpiece attached to a one-way valve, blocking the flow of the air until the patient produces sufficient expiratory pressure. It is meant to strengthen the expiratory and submental muscles by increasing the physiologic load [428]. This treatment has shown significant effects on swallowing safety in a RCT in Parkinson patients [229], has improved swallowing safety and feeding status in a RCT in subacute stroke patients [448], has been associated with positive effect on swallowing-related muscle strength in elderly participants [449], and has been found to improve swallow kinematics, in particular hyoid displacement, in a cohort study with pre-post design in ALS patients [450]. No effect on swallowing parameters and related outcomes were observed in patients with Huntington’s disease [451].

The effortful swallow is used for patients who present with clinically significant residue in the valleculae and/or pyriform sinuses as well as for patients who may have decreased airway closure [430]. Physiologically, the effortful swallow has been shown to increase hyolaryngeal excursion, duration of hyoid elevation and UES opening, laryngeal closure, lingual pressures, peristaltic amplitudes in the distal esophagus and pressure and duration of tongue base retraction in healthy subjects [452-455]. Effects over time were studied in a RCT in healthy individuals. The main finding was that lingual pressure increased, albeit insignificantly, after four weeks of exercising the effortful swallow [456]. In addition, a second small cohort study assessed the effect of this exercise in patients with Parkinson’s disease and found improved pharyngeal manometric pressure after a two-week treatment period [457].

The Masako maneuver involves swallowing while protruding the tongue beyond the lips, holding it between one’s teeth. It is meant to have a strengthening effect on the tongue and the pharyngeal walls after a period of training [458]. Studies in healthy subjects did not find immediate effects on swallowing physiology [459,460]. A RCT including healthy subjects exposed to a four-week training with the Masako maneuver or a control task found no effect on the swallow [461]. In a small RCT recruiting subacute stroke patients, the Masako maneuver was compared with neuromuscular electrical stimulation. In that trial, both groups showed improvement of swallowing function, however, since a control group was missing, these results need further confirmation [462].

The Mendelsohn maneuver is a technique used for patients with decreased hyolaryngeal excursion and/or decreased duration of UES opening and is frequently combined with some form of biofeedback to help the patient perform it. To execute this maneuver, patients are instructed to keep the thyroid cartilage for several seconds in an elevated position before finishing the swallow [430]. Long-term effects of the Mendelsohn maneuver have been evaluated in one RCT in stroke patients [463,464]. In that study, the authors could demonstrate that hyoid movement and upper esophageal sphincter opening improved after treatment.

The super-supraglottic swallow is used as compensatory maneuver for patients with reduced airway closure. This maneuver involves a person holding a tight breath, swallowing while keeping the airway closed, then immediately coughing after the swallow. It has been shown in several studies that the super-supraglottic swallow has immediate effects on swallowing physiology [465-467], but there are no studies investigating long-term effects of this maneuver [428].

Reflecting the fact that patients suffering from OD have a highly variable pattern of specific swallowing abnormalities, more complex treatment approaches combining different adaptive, compensatory and rehabilitative techniques have been employed in a variety of studies. In their systematic review Speyer and co-workers summarized 4 RCTs and 27 nonrandomized trials most of which showing significant improvements of swallowing function and related endpoints [429]. The largest RCT to date has been performed by Carnaby et al. [468] in stroke patients. The authors
compared the change of dietary status after usual care (N = 102), standard low-intensity intervention (N = 102) and standard high-intensity intervention (N = 102). After six months, the percentage of patients returning to a normal diet was 56% for usual care, 64% for standard low-intensity and 70% for standard high-intensity treatment. In patients who received standard therapy (either low or high intensity) medical complications, chest infections and death or institutionalization decreased significantly. Recently, two systematic treatment programs have been evaluated in non-randomized trials. The McNeill dysphagia treatment protocol improved swallowing physiology in an observational study [469], as well as diet and clinical swallowing ability in a case–control and a cohort study [470,471]. The intensive dysphagia rehabilitation protocol was tested in a small observational study and led to an improvement of aspiration severity and level of oral intake [472].

7.3. Clinical Question 40: Which types of neurostimulation treatment approaches are available for patients with oropharyngeal dysphagia?

Recommendation 83:

Prior to initiating any stimulation therapy targeting OD, patients should receive a clinical swallow exam or, preferentially, an instrumental swallow evaluation. This evaluation should be repeated after the treatment has been finished.

Grade of recommendation: GPP — strong consensus (100% agreement)

Recommendation 84:

Due to the limited number of evidence, all stimulation treatments should preferably be carried out within clinical trials.

Grade of recommendation: GPP — strong consensus (95% agreement)

Recommendation 85:

There is evidence that neuromuscular electrical stimulation (NMES) improves swallowing function in patients with OD of different etiologies. NMES applied together with behavioral swallowing treatment is superior to behavioral swallowing treatment alone, in particular in post-stroke OD. NMES may be used alone, or preferentially, as adjunct to behavioral swallowing treatment in patients with OD.

Grade of recommendation: B — strong consensus (100% agreement)

Commentary:

Apart from traditional swallowing training and bolus modification strategies, several adjunctive treatment options have been explored recently. These treatments include surface neuromuscular electrical stimulation (NMES), pharyngeal electrical stimulation (PES), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). NMES and PES target the neuromuscular system peripherally, rTMS and tDCS focus on the central swallowing network. Although these treatment options have been applied frequently and in different patient populations, there is still a lack of large multicenter RCTs with meaningful clinical endpoints.

NMES is used to activate sensory nerves or muscles involved in swallowing function through stimulation of axonal motor nerve endings and muscle fibers. Its mechanism of action is thought to include accelerating the development of muscle strength and promoting central nervous system recovery. This treatment that is usually applied as adjunct to behavioral swallowing therapy has been evaluated in several mostly small studies (case control and cohort studies as well as single-center RCTs) including patients with OD of different etiologies, predominantly post-stroke. So far, three meta-analyses have been performed that all point towards a modest effect of NMES both on swallowing physiology as well as on feeding status [473–475]. These findings have been corroborated in two recent RCTs not included in these meta-analyses. Park et al. showed improved hyoid-movement in subacute stroke patients being treated with NMES in combination with effortful swallowing compared to effortful swallowing alone [476]. Terre and Mearin found improved feeding status in patients with OD after stroke or traumatic brain injury when being exposed to NMES and conventional swallowing therapy compared to conventional swallowing therapy alone [477].

Non-invasive brain stimulation is based on the principle of neuroplasticity, best defined as changes in neuronal pathways to increase neural functioning via synaptogenesis, reorganization, and network strengthening and suppression. The two most commonly used techniques to directly target cortical areas are tDCS and rTMS, whereas PES applies stimulation to pharyngeal structures, indirectly targeting the pharyngeal motor and sensory cortices and related brain areas. Both tDCS and rTMS have been evaluated in several small RCTs and cohort studies, most of them focusing on patients with OD due to acute or chronic stroke. Three meta-analyses have been performed, each with a slightly different sub-selection of studies [478–480]. Concordant conclusion of all three studies was that noninvasive brain stimulation was associated with sustained improvement of swallowing function compared to sham treatment. PES has successfully been used in three RCTs recruiting dysphagic stroke patients and one RCT devoted to patients with multiple sclerosis suffering from OD [481–483]. Apart from that, a meta-analysis confirmed a positive treatment effect of PES [484]. However, in a large multicenter RCT of subacute dysphagic stroke patients, PES did not improve dysphagia when compared to sham treatment [485].

7.4. Clinical Question 41: Which pharmacological treatments are available for patients with oropharyngeal dysphagia?

Recommendation 86:

Prior to considering a pharmacological treatment in a patient with OD, a clinical swallow exam or, preferentially, an instrumental swallow evaluation should be carried out.

Grade of recommendation: GPP — strong consensus (100% agreement)

Recommendation 87:

Pharmacological treatment options, in particular TRPV1 agonists and dopaminergic agents, may be used as adjunct to behavioral swallow therapy in patients, in whom a delayed swallow reflex had been identified as main feature of OD.

Grade of recommendation: B — strong consensus (100% agreement)

Recommendation 88:

Due to the limited evidence with regards to clinical endpoints, pharmacological treatment decisions need to be individualized and have to be based on a careful risk-benefit analysis.
Grade of recommendation: GPP — strong consensus (100% agreement)

Commentary:

Pharmacological treatment of OD involves the use of drugs that stimulate the neural pathways of deglutition either on the peripheral sensory level or at different levels of the central nervous system [486]. Classes of pharmacological agents that have been evaluated for their potential to improve disordered swallowing are TRPV1 (transient receptor potential cation channel subfamily V member 1) agonists, angiotensin-converting-enzyme-inhibitors and dopaminergic agents. Overall, the potential of this treatment approach has not been fully explored, and in particular sufficiently powered multicenter RCTs with clinically relevant endpoints are required.

TRPV1 agonists, in particular capsaicinoids and piperine, stimulate TRPV1 receptors expressed at free nerve endings of the superior laryngeal nerve and the glossopharyngeal nerve [487,488]. Several observational studies, case control studies and one RCT [489–494] have shown that TRPV1 agonists improve the safety of the swallow by decreasing the latency of the swallow reflex, by shortening laryngeal vestibule closure time and by enhancing hyoid motion. However, studies with clinical endpoints have not been conducted so far.

Loss of dopaminergic neurons in the central nervous system due to stroke or neurodegenerative diseases is known to contribute to OD and is in particular associated with a decreased swallow reflex [495]. Application of levodopa has been shown to normalize the onset of the pharyngeal swallow in a RCT with cross-over design that recruited patients with post-stroke OD [496]. A second RCT focusing on a similar study population found that nocturnal aspiration episodes were reduced by treatment with either amantadine or cabergoline (dopamine receptor agonist) [497]. Finally, in the largest RCT to date, Nakagawa and co-workers showed that treatment with amantadine significantly decreased the rate of pneumonia in post-stroke patients over the study period of three years [498].

ACE inhibitors are widely used antihypertensive drugs that can cause a dry cough as a side effect. One of the mechanisms for this side effect is the decreased degradation of substance P, which is released from sensory nerve terminals in the nasopharynx. Substance P in turn is known to enhance the swallow reflex and there is evidence that decreased sputum levels of this neurotransmitter are associated with aspiration pneumonia [499]. In line with this pathophysiological consideration, ACE inhibitors have been shown to decrease the latency of the swallow reflex, to increase the involuntary swallow frequency and to protect patients from nocturnal aspirations [500–502]. The subsequent and clinically most relevant question whether ACE inhibitors also reduce the incidence of aspiration pneumonia has no clear answer to date. A recent meta-analysis including 5 multicenter RCTs, 8 cohort and nested-case control studies and 6 case–control studies points towards a protective role of ACE inhibitors in this context [503]. However, a very recent multicenter RCT randomizing tube-fed post-stroke patients to 2.5 mg Lisinopril or placebo was prematurely terminated because of an excess of mortality in the intervention group. There was no difference in the incidence of pneumonia [504]. See supplementary data for Clinical Questions 38–41.

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Conflict of Interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict of interest forms are stored at the ESPEN guideline office and can be reviewed by ESPEN members with legitimate interest upon request to the ESPEN executive.

Abbreviations

ALS Amyotrophic Lateral Sclerosis
ALSFRS Amyotrophic Lateral Sclerosis functional rating scale
ALSFRS-R Amyotrophic Lateral Sclerosis functional rating scale revised
ALSSS Amyotrophic Lateral Sclerosis swallowing severity scale
BIA bioelectrical impedance
BMD bone mineral density
BMI body mass index
CBA clinical bedside assessment
CNS central nervous system
DBS deep brain stimulation
DEXA dual-energy X ray absorptiometry
DHA docosahexaenoic acid
DYMUS Dysphagia in multiple sclerosis
EAT-10 eating assessment tool
EDSS expanded disability status scale
EMST expiratory muscle strength training
EN enteral nutrition
EPA eicosapentaenoic acid
FEES Fiberoptic endoscopic evaluation of swallowing
FFM free fatty mass
FM fat mass
FOOD feed or ordinary food
FVC forced vital capacity
LOS length of stay
MDT-PD Munich dysphagia test-Parkinson's disease
MNA mini-nutritional assessment
MND motor neuron disease
MRI magnetic resonance imaging
MS multiple sclerosis
MUST malnutrition universal screening tool
OD oropharyngeal dysphagia
ONS oral nutritional supplementation
PA phase angle
PD Parkinson’s disease
PEG percutaneous endoscopic gastrostomy
PN parenteral nutrition
PUFA poly-unsaturated fatty acids
QoL quality of life
RCT randomized controlled study
REE resting energy expenditure
RIG radiologically inserted gastrostomy
SDQ swallowing disturbance questionnaire
TEE total energy expenditure
TRPV1 transient receptor potential cation channel subfamily V member 1
VAST video-assisted swallowing therapy
VFM videofluoromanometry
VFS video-fluoroscopy
VVST volume-viscosity swallow test
WL weight loss
Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.09.003.

References


