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ESPEN guideline clinical nutrition in neurology

Rosa Burgos [a, *], Irene Bretón [b], Emanuele Cereda [c, d], Jean Claude Desport [e], Rainer Dziewas [f], Laurence Genton [g], Filomena Gomes [h], Pierre Jésus [e], Andreas Leischker [i], Maurizio Muscaritoli [j], Kalliopi-Anna Poulia [k], Jean Charles Preiser [l], Marjolein Van der Marck [m], Rainer Wirth [n], Pierre Singer [o], Stephan C. Bischoff [p]

[a] Nutritional Support Unit, University Hospital Vall d'Hebron, Barcelona, Spain
[b] Nutrition Unit, University Hospital Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain
[c] Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[d] Fondazione Grigioni per il Morbo di Parkinson, Milano, Italy
[e] Nutrition Unit, ALS Centre, University Hospital of Limoges, Limoges, France
[f] Department of Neurology, University Hospital Münster, Germany
[g] Clinical Nutrition, Geneva University Hospitals, Geneva, Switzerland
[h] Cereneo (Center for Neurology and Rehabilitation) and University Department of Internal Medicine, Kantonsspital Aarau, Switzerland
[i] Department of Geriatrics, Alexianer Hospital Krefeld, Krefeld, Germany
[j] Department of Clinical Medicine, Sapienza, University of Rome, Rome, Italy
[k] Department of Nutrition, Laikon General Hospital, Athens, Greece
[l] Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium
[m] Department of Geriatric Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
[n] Department of Geriatric Medicine, Marien Hospital Herne, Ruhr-University Bochum, Germany
[o] Department of General Intensive Care and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Tel Aviv University, Petah Tikva, Israel
[p] Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

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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.

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.

* Corresponding author. Nutritional Support Unit, University Hospital Vall d'Hebron, Pg Vall d'Hebron 119-129, 08025, Barcelona, Spain.
E-mail address: rburgos@vhebron.net (R. Burgos).

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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 broad 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

Table 1
Example of the search strategy.

Clinical Question 35. 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?
P: patients with acute stroke
I: enteral nutrition or enteral feeding or tube feeding
C: stroke patients with ONS or with oral texture-modified diet alone
O: complications, length of stay, infectious complications, poor outcome, mortality, energy intake, body weight, quality of life.
First search:
Two guidelines on nutritional support in stroke patients have been published in 2013 [DGEM Guidelines [19] and Royal College of Physicians [20]], both with literature review covering data until December and October 2011, respectively.
One systematic review of the literature was published in 2012 [21] including a review of the literature until July 2011.
Second search:
Strategy was dated from December 2011 until June 2016:
Stroke [MeSH] OR Stroke [Title/Abstract] AND enteral feeding [Title/Abstract]
24 articles retrieved.
18 non-relevant by reading title
2 non-relevant after reading abstract
1 review article
3 relevant articles selected. None intervention study, all were observational studies.

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 2
Levels of evidence (SIGN grading system) [22].

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1−	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	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
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

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

a. Grades of recommendation

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

b. Forms of recommendation

Judgment	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

- 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 impairs 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 riluzole 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 = 1.68 [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: 0.83–0.96]; p = 0.003) [28]. Bioelectrical impedance (BIA) with validated formula compared to dual-energy X ray absorptiometry (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]. Kasarksis 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]. Shimitzu 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/m^2), weight stabilization in those with a BMI between 25 and 35 kg/m^2, and weight loss in patients with a BMI > 35 kg/m^2 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/m^2 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 sail 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 the 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 [58,62,63]. 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 presence 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/m^2) malnutrition was found in 0%–1.1%, 10.1% (<20 kg/m^2) and 8.7%–13.0% (<18.5 kg/m^2 if age<70 years and <21 kg/m^2 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/m^2) 2.1%–20.1%, (<20 kg/m^2) 16.1%–26.4% and (<18.5 kg/m^2 if age<70 years and <21 kg/m^2 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/m^2) and 27.4%–53.0% (<20 kg/m^2) 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, videofluoromanometry 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 effectivity 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].

Oropharyngoesophageal 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, videofluoromanometry 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 extremity 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-esophageal 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.

Videofluoromanometric 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. Goeleven [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 (3×200 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 ($p = 0.01$) [99]. 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.

3.10. Clinical Question 10: Does enteral nutrition (EN) improve quality of life in ALS patients?

Recommendation 15:

EN may positively affect some aspects of quality of life. Since the impact of EN on quality of life of ALS patients is difficult to estimate and has not been adequately addressed in available studies, we recommend that the *pros* and *cons* of EN are adequately discussed with the patient, family and caregivers when EN is proposed.

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

Commentary:

Much can be done to alleviate the large variety of symptoms that ALS patients suffer [98], also as a consequence of swallowing impairment. As a result of dysphagia, food and fluid intakes are gradually decreased because of the fear of coughing and choking and because the time required for eating becomes unsustainably long [35,96]. In addition, an EN access route is useful to ensure sufficient fluid intake and administration of medication.

Although there is consensus that EN represents the medical nutrition therapy modality of choice in ALS patients in whom nutritional needs cannot be met with oral feeding [96], quality of life issues such as the loss of the hedonic component of feeding, appetite, thirst, psychological discomfort for the medicalization of feeding should be considered and discussed when proposing EN [98]. The benefits of EN through a PEG appear to be critically dependent on the interval occurring from the diagnosis of ALS to PEG placement and, of course, by the clinical presentation and the consequent evolution of the disease. Only two controlled studies have evaluated changes in quality of life after EN. Neither of these showed clear evidence for improved quality of life after PEG. Mazzini et al. [72] related impressions from patients that their quality of life improved after PEG but reported no concrete data. Mitsumoto et al. [101] reported quantitative results, based on percent of patients who responded affirmatively or negatively to specific questions about quality of life after PEG. The majority of the patients (79%) reported that stabilized nutritional and hydrational status was the most positive effect of PEG. A minority of PEG patients (17%) reported improved psychological wellbeing with regard to nutrition and 28% listed less fatigue or less time spent on meals and medications [101]. A Cochrane review from Katzberg et al. concluded that quality of life issues have not been adequately addressed in studies and it needs more attention [102]. See supplementary data for Clinical Question 10.

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 EFNS 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 hat 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 orofacial 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 prospective way.

Verschueren 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. Gastrointestinal 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 overweight 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 provision of active form 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 antioxidant 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/m^2, 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 VFSS. 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, buccolinguofacial 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 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 expiratory muscle 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. Diverse 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 [232], 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 suprahyoid 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 neurorehabilitation non-invasive technique, has been used to modulate neural activity in targeted focal brain regions. Murdoch 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.

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

Commentary:

Constipation is the most frequent non-motor symptom and manifestation of gastro-intestinal dysfunction in PD patients [124,131,246]. It is mainly the consequence of neurodegenerative process involving the enteric nervous system but it could be also the side effect of certain PD medications (mainly dopamine agonists and anticholinergics) [131]. Furthermore, reduced physical activity associated with motor impairment is considerable contributing factor [124]. Nonetheless, it is worth mentioning that defecatory dysfunction in PD may be due not only to slow colonic transit but also to pelvic floor dyssynergia [124,131,246]. Unfortunately, few treatment options either pharmacologic or non-pharmacologic have been tested and investigated in this patient population. Accordingly, the use of the same treatment algorithm for patients with idiopathic chronic constipation is recommended also for PD patients [131] [131,247]. Non pharmacological lifestyle modifications could be proposed to improve colonic transit. Common nutritional management strategies include the increase of fiber and fluid intake [124,131,247]. In a small RCT (n = 7) with high risk of bias the use psyllium was found to increase the total number of bowel movements but did not improve other parameters of defecation (stool consistency, straining effort, pain on defecation, or completeness of evacuation) [248]. After a positive preliminary experience [249], a recent large RCT (n = 120) with low risk of bias has demonstrated that, compared to placebo, the daily consumption of a fermented milk containing probiotics and prebiotic fiber for 4 weeks resulted not only in an increased number of complete bowel movements but also in an improvement of stool consistency, as well as in a larger reduction in the use of laxatives [250]. Despite the fact that the experimental product used in this trial is not available on the market, the use of probiotics as adjuvant treatment for constipation could be extensively recommended to PD patients due to its safety profile. See supplementary data for Clinical Question 24.

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.

Weight loss, malnutrition and even cachexia are well-recognized features of patients with MS [251]. The possible causes of weight loss and malnutrition in MS have been well identified: reduced mobility and fatigue, inappropriate diet, physical difficulty for eating or drinking, poor appetite, poor sight, reduced cognition and dysphagia. Medical nutrition therapy should be guided by the identification of the cause of weight loss and malnutrition in each case. 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)

Recommendation 35:

We do not recommend supplementation of n-3 fatty acids for the prevention of MS and other demyelinating diseases.

Grade of recommendation: 0 – strong consensus (95% 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 relationship 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 neuroimmunological 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 $\geq$ 30 kg/m^2) had a two-fold increased risk of developing MS compared to women with BMI between 18.5 and 20.9 kg/m^2 (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. [284] 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 ($p = 0.09$).

Shaygannejad 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.

Soilu-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 to 0.26 in the vitamin D group, and from 0.51 to 0.28 in the placebo group, $p = NS$). There was no significant difference in the time to the first relapse between groups. The proportion of relapses treated with methylprednisolone was similar in both treatment arms.

Two studies have evaluated the effect of high dose vitamin D versus low dose vitamin D [287,288].

Stein et al. [287] compared in a 6 months' double-blind placebo-controlled high-dose vitamin D2 (6.000 IU targeting 25-OH vitamin D 130–175 nM) with 1.000 IU daily vitamin D2. The primary endpoint was new MRI lesions, and as a secondary endpoint, relapse rate was evaluated. They included 23 patients in the trial, of whom 19 were on disease-modifying drugs (interferon or glatiramer). No significant differences were detected either in the primary endpoint, or in relapse rate during the trial (there were 4 relapses with high-dose D2 vs none with low-dose D2, $p = 0.04$)

Golan et al. [288] assessed the effect of 800 IU of vitamin D3 per day vs 4.370 IU/day in a randomized, double blind study including 45 IFNβ-treated MS patients during one year. The primary endpoint was the control of flu-like symptoms, and as a secondary endpoint, they assessed relapse rate of the disease. Both groups were similar at baseline with respect to relapses and annualized relapse rate during the year preceding randomization. At the end of the study, no differences were found in the annual relapse rate in both groups.

One systematic review of six trials [289] reported that no studies had results suggestive of a benefit of vitamin D supplementation for reducing relapse rates in MS patients. Another systematic review and meta-analysis [290] reported that there was no significant difference in the pooled odds of relapse between high dose vitamin D supplements and low dose or placebo.

In conclusion, the RCT published to date investigated the use of vitamin D supplements of various doses and formulations and with or without concomitant therapy for MS treatment and with calcium supplements. The duration of treatment also varied between trials.

Recommendation 42:

Supplementation with omega-3 fatty acids should not be recommended in MS patients to decrease the number and severity of relapses. Supplementation with omega-6 fatty acids could be of some possible benefit in terms of decreasing the number and severity of the relapses.

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

Commentary:

The hypothesis that a change in dietary fat can modify the course of MS is based on epidemiological and experimental studies. MS is more prevalent in populations with a high intake of saturated fats. Furthermore, PUFA, particularly omega-3 fatty acids have an immunomodulatory and anti-inflammatory role that could influence the course of the disease. The intake of omega-3 fatty acids from fish oil can reduce the production of pro-inflammatory prostaglandins and leukotrienes derived from arachidonic acid.

Until now, non-controlled and controlled clinical trials of PUFA supplementation in patients with MS have provided mixed results. These studies have important limitations in design and selection of outcome measures, and these factors might partially explain the inconsistent results [259–261]. The inclusion of both patients with relapsing MS and patients with chronic, progressive disease provides 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 PUFA 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 PUFA 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 Kinqwell 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. Clavé 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: Clacagno 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 manofluoroscopy 30 of the 73 MS patients with permanent dysphagia in their study, and they described deficiency of the oral phase in all patients, 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. Terré-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 oropharyngeal 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 2000 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 [19,336–346]. 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 [349,356–359]. 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)

Commentary:

The majority of the studies [21] which have explored the effect of medical nutrition therapy strategies for stroke patients (some of them conducted in individuals who are malnourished or at risk of malnutrition) tend to provide an undifferentiated form of medical nutrition therapy for all the individuals of the intervention group, e.g. using only oral nutritional supplements for patients without swallowing problems. Only one study has evaluated the effect of an individualized nutrition treatment plan in this population, involving different forms of medical nutrition therapy according to the individual needs of each patient.

Ha and her colleagues [364] selected a group of hospitalized acute stroke patients aged > 65 years who were assessed as being undernourished (using anthropometric values) or at nutritional risk (using a modified version of the Malnutrition Universal Screening Tool). These patients were allocated to the intervention group, where they received an individualized nutritional treatment plan detailing type, amount and route of feeding (including oral nutritional supplements and enteral tube feeding) for each patient, or to the control group, where patients received routine care at the discretion of the attending physician. In the intervention group, the nutrition plan was adjusted as necessary, according to the recorded and calculated dietary intake for each patient, and individual advice to prevent malnutrition was delivered before discharge. Outcomes were assessed at 3 months after study entry. Results showed statistically significant differences between the groups in favor of the intervention group with regards to energy intake [5010 (SD 1376) kJ/day versus 4373 (SD 1268) kJ/day; P = 0.032), as well as change in weight (20.7% versus 36.4% had ≥5% weight loss; 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 results 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 dietitian 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. The 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 puréed 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 texture 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 ordered thickened liquids take additional fluids without thickener [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 thickener 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 thickener 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 (χ [2] = 5.091, $p = 0.024$), but no differences between groups with regard to diagnoses of dehydration (χ [2] = 0.884, $p = 0.347$) or constipation (χ [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 [326] kcal versus 1569 [260] kcal, $P < 0.024$), non-starch polysaccharide (6.3 [1.7] g versus 8.3 [2.7] g, $P < 0.02$) and fluid (1196 [288] ml versus 1611 [362] ml, $P < 0.002$) when compared with residents on a standard texture diet [379].

In a 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 kJ/day, $P < 0.0001$) and protein (40 versus 60 g/day, $P < 0.003$) 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 kJ, $P < 0.0001$; 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 bridle is not feasible or not tolerated, early feeding via PEG should be started.

Grade of recommendation: GPP – 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 dysphasia, 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 participants 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.

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. Dziewas 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.

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 74:

There is evidence that using thickened liquids fails to substantially increase fluid intake in persons with OD. Liquid thickening should be applied in patients with OD aspirating on liquids, however, liquid intake needs to be closely monitored since there is a high risk of insufficient oral intake.

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

Recommendation 75:

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

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

Recommendation 76:

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 "thin", "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 suprahyoid 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 strengths and endurance of the suprahyoid 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.

Expiratory 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 coworkers 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 preferentially 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 subselection 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 absortiometry
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

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ESPEN Guideline

ESPEN practical short micronutrient guideline

Mette M. Berger [a, *, 1], Alan Shenkin [b, 1], Oguzhan Sıtkı Dizdar [c], Karin Amrein [d], Marc Augsburger [e], Hans-Konrad Biesalski [f], Stephan C. Bischoff [g], Michael P. Casaer [h], Kursat Gundogan [i], Hanna-Liis Lepp [j], Angélique M.E. de Man [k], Giovanna Muscogiuri [l, m], Magdalena Pietka [n], Loris Pironi [o, p], Serge Rezzi [q], Anna Schweinlin [g], Cristina Cuerda [r]

[a] Faculty of Biology & Medicine, Lausanne University, Lausanne, Switzerland
[b] Institute of Aging and Chronic Disease, University of Liverpool, Liverpool, UK
[c] Department of Internal Medicine and Clinical Nutrition Unit, University of Health Sciences Kayseri City Training and Research Hospital, Kayseri, Turkey
[d] Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria
[e] University Centre of Legal Medicine Lausanne-Geneva, Lausanne University Hospital and University of Lausanne, Geneva University Hospital and University of Geneva, Lausanne-Geneva, Switzerland
[f] Institute of Nutritional Science, University of Hohenheim, Stuttgart, Germany
[g] Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany
[h] KU Leuven, Department of Cellular and Molecular Medicine, Laboratory of Intensive Care Medicine, Leuven, Belgium
[i] Division of Intensive Care Medicine, Department of Internal Medicine, Erciyes University School of Medicine, Kayseri, Turkey
[j] North Estonia Regional Hospital, Tallinn, Estonia
[k] Department of Intensive Care Medicine, Research VUmc Intensive Care (REVIVE), Amsterdam Cardiovascular Science (ACS), Amsterdam Infection and Immunity Institute (AI&II), Amsterdam Medical Data Science (AMDS), Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands
[l] Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università di Napoli (Federico II), Naples, Italy
[m] United Nations Educational, Scientific and Cultural Organization (UNESCO) Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy
[n] Pharmacy Department, Stanley Dudrick's Memorial Hospital, Skawina, Poland
[o] Department of Medical and Surgical Sciences, University of Bologna, Italy
[p] Centre for Chronic Intestinal Failure, IRCCS AOUBO, Bologna, Italy
[q] Swiss Nutrition and Health Foundation, Epalinges, Switzerland
[r] Departamento de Medicina, Universidad Complutense de Madrid, Nutrition Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

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SUMMARY

Background: Trace elements and vitamins, named together micronutrients (MNs), are essential for human metabolism. The importance of MNs in common pathologies is recognized by recent research, with deficiencies significantly impacting the outcome.
Objective: This short version of the guideline aims to provide practical recommendations for clinical practice.
Methods: An extensive search of the literature was conducted in the databases Medline, PubMed, Cochrane, Google Scholar, and CINAHL for the initial guideline. The search focused on physiological data, historical evidence (for papers published before PubMed release in 1996), and observational and/or randomized trials. For each MN, the main functions, optimal analytical methods, impact of inflammation, potential toxicity, and provision during enteral or parenteral nutrition were addressed. The SOP wording was applied for strength of recommendations.
Results: The limited number of interventional trials prevented meta-analysis and led to a low level of evidence for most recommendations. The recommendations underwent a consensus process, which resulted in a percentage of agreement (%): strong consensus required of >90 % of votes. Altogether the

* Corresponding author.
E-mail addresses: Mette.Berger@unil.ch (M.M. Berger), shenkin@liverpool.ac.uk (A. Shenkin), oguzhansitki.dizdar@sbu.edu.tr (O.S. Dizdar), karin.amrein@medunigraz.at (K. Amrein), Marc.Augsburger@chuv.ch (M. Augsburger), hans-k.biesalski@uni-hohenheim.de (H.-K. Biesalski), bischoff.stephan@uni-hohenheim.de (S.C. Bischoff), michael.casaer@uzleuven.be (M.P. Casaer), kursatgundogan@gmail.com (K. Gundogan), liis.lepp@gmail.com (H.-L. Lepp), ame.deman@amsterdamumc.nl (A.M.E. de Man), giovanna.muscogiuri@gmail.com (G. Muscogiuri), magpietka@gmail.com (M. Pietka), Loris.pironi@unibo.it (L. Pironi), serge.rezzi@nutritionhealthfoundation.ch (S. Rezzi), anna.schweinlin@uni-hohenheim.de (A. Schweinlin), cuerda.cristina@gmail.com (C. Cuerda).
[1] Shared first authors.

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guideline proposes 3 general recommendations and specific recommendations for the 26 MNs. Monitoring and management strategies are proposed.
Conclusion: This short version of the MN guideline should facilitate handling of the MNs in at-risk diseases, whilst offering practical advice on MN provision and monitoring during nutritional support.

Abbreviation list

25(OH)D	25-hydroxyvitamin-D
AA	ascorbic acid
AI	adequate intake
AKI	acute kidney injury
CoQ10	Coenzyme Q10
CRP	C-reactive protein
DFE	dietary Folate Equivalents
DHAA	dehydroascorbic acid
DRI	dietary reference intake
EAR	estimated average requirement
EN	enteral nutrition
FAD	flavin adenine dinucleotide
FSMP	foods for special medical purposes
GPX-3	plasma glutathione peroxidase
ICU	intensive care unit
IM	intramuscular
IV	intravenous
MADD	multiple acyl-Coenzyme A dehydrogenase deficiency
MN	micronutrient
NAD	nicotinamid adenine dinucleotide
PLP	pyridoxal phosphate
PN	parenteral nutrition
RBC	red blood cells
RCT	randomized controlled trial
RDA	recommended dietary allowances
ROS	reactive oxygen species
ThDP	thiamine diphosphate
TPP	thiamine pyrophosphate
UL	tolerable Upper Intake Level

1. Introduction

Micronutrients, a generic term for trace elements and vitamins, are essential components of nutrition in health and disease. For the general population, international recommendations are available in the form of recommended dietary allowances (RDA), or more recently, as DRI (Dietary Reference Intakes). However, there are yet no standardized procedures for the determination of requirements or recommendations for intake for patients with acute and chronic diseases. To assist clinicians, the recent ESPEN guideline [1] provides practical recommendations for the assessment of the micronutrient (MN) status in adult patients and information about basic or increased amounts, covering the fields of enteral and parenteral nutrition.

Status assessment is based on the patient's history, clinical assessment, and laboratory investigations. The guideline emphasizes the difficult interpretation of low micronutrient levels in the presence of inflammation, with the necessity to assess the magnitude of a concomitant inflammatory response [2,3].

The original document is very long since it includes extensive biochemistry physiology and advice on each of the MN. Therefore, the present abbreviated guideline is a summary focusing on the recommendations and clinical practice applications. The iteration of the guideline is of even higher importance after the publication by the World Health Assembly (WHA) of their resolution to accelerate efforts regarding micronutrient provision with safe supplementation.

2. Methods

The ESPEN micronutrient-working group attempted to apply the 2015 standard operating procedures for ESPEN guidelines and consensus papers with PICO questions (patient, intervention, comparator, outcome) [4], but failed due to a lack of intervention trials, resulting in structured reports for each MN based on systematic review. The literature was searched for evidence regarding 1) different diseases (see § 3), 2) therapeutic interventions (enteral nutrition, parenteral nutrition, renal replacement therapy), and 3) special periods of life (pregnancy, elderly).

The SIGN evaluation system (Scottish Intercollegiate Guidelines Network) [4] was applied to the available interventional trials. The recommendations were created and graded into the four listed classes (A/B/0/GPP). When solid evidence coming from biochemistry and physiology was extrapolated to clinical settings, it allowed the upgrading of recommendations to an A or B level, enabling the use of "shall" or "should" in the recommendation formulation. Dose recommendations based on existing RDA are attributed a level A as they are based on internationally validated evidence, whereas those based on DRI are given a level B.

As many recommendations are supported by limited evidence, they underwent a consensus process, which resulted in a percentage of agreement (%). The "strong consensus "qualification required >90 % of agreement, and "consensus" was defined as an agreement of 75–90 % of the experts and participants [5]. There were two rounds of votes. In case of agreement <90 % during the first Delphi vote, the recommendations were thoroughly reviewed and -if necessary-reformulated. All recommendations with substantial changes were voted on again. Recommendations with less than 75 % agreement were discarded.

For further details on methodology of the original guideline development, see the full version of the ESPEN guideline [1] and the ESPEN standard operating procedures (SOP) [4].

When transforming the original guideline to the practical version, the texts were reduced to the basic principles, and information on toxicity. The analytical aspects detailed in the main document were deleted, with focus mainly on the clinical aspects of deficiency and eventual toxicities. Please refer to the initial guideline for more detailed information.

The meaning of the recommendations has not been changed. In a few cases, it was necessary to adapt the wording because feedback from users since the publication of the original version showed that some of the recommendations were worded

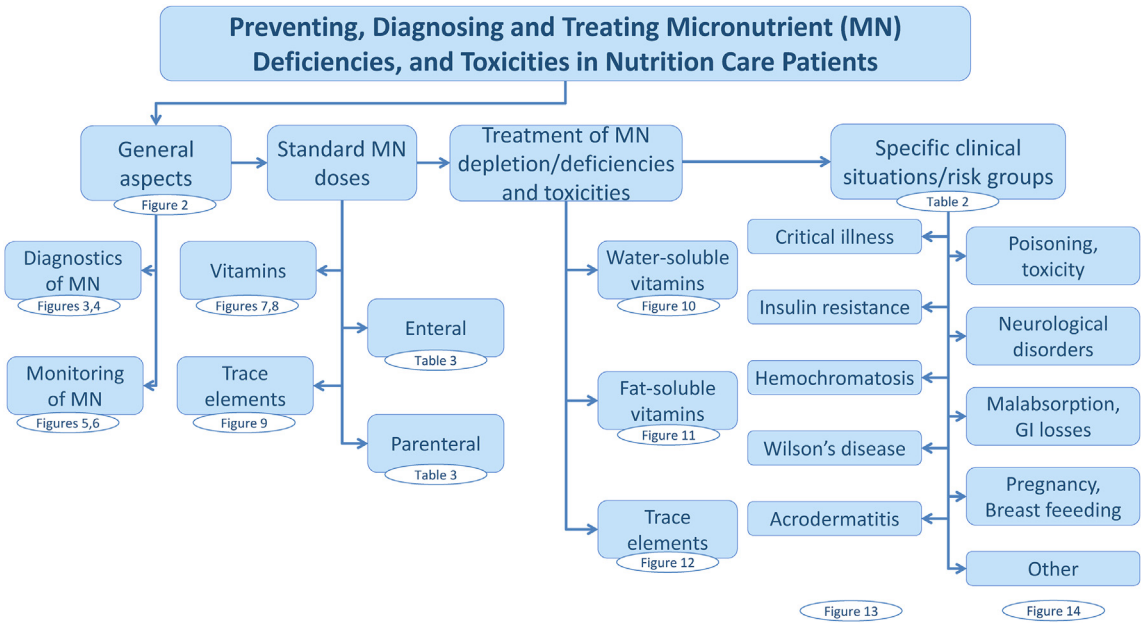

Fig. 1. Structure of the practical Guideline of Micronutrients; Carnitine, Choline and Co-10 have no defined DRIs (they are covered in full version of MN guideline). Abbreviation: MN, micronutrients.

ambiguously. The wording of these recommendations has been made more precise. The recommendations concerned are 2, 4.1, 4.6, 5.3, 7.4, 7.7, 12.6, 15.5, 16.1, 18.1, 20.2, 21.3, 23.3. The transformation to a practical version includes a graphical presentation as flow charts (Figs. 1 and 2). In these flow charts, the recommendations are rearranged according to the topic diagnostics (Figs. 3 and 4), monitoring (Figs. 5 and 6), standard doses for enteral and parenteral nutrition (Figs. 7–9), depletion, deficiency, and toxicity (Figs. 10–12), as well as special situations (Figs. 13 and 14) for which some additions were made for completeness. The respective position in the flow charts is indicated for each recommendation in brackets. The literature recommendations with grade A, B, or 0 are based on is cited directly below the respective recommendations.

3. Micronutrients status

Defining precisely suboptimal or deficient status is the basis for therapeutic intervention. The term "deficiency" has been used too broadly, being often used as soon as the laboratory returns blood values below the local or international reference range. The new Table 1 provides the definitions that are proposed to qualify the status and the therapeutic interventions. Particular attention is drawn to the definitions of 'deficiency' and 'depletion'.

3.1. Requirements, dosage and treatment considerations

The DRIs are fundamental to inform national nutrition policies and regulations. We have therefore used the definitions of the Food

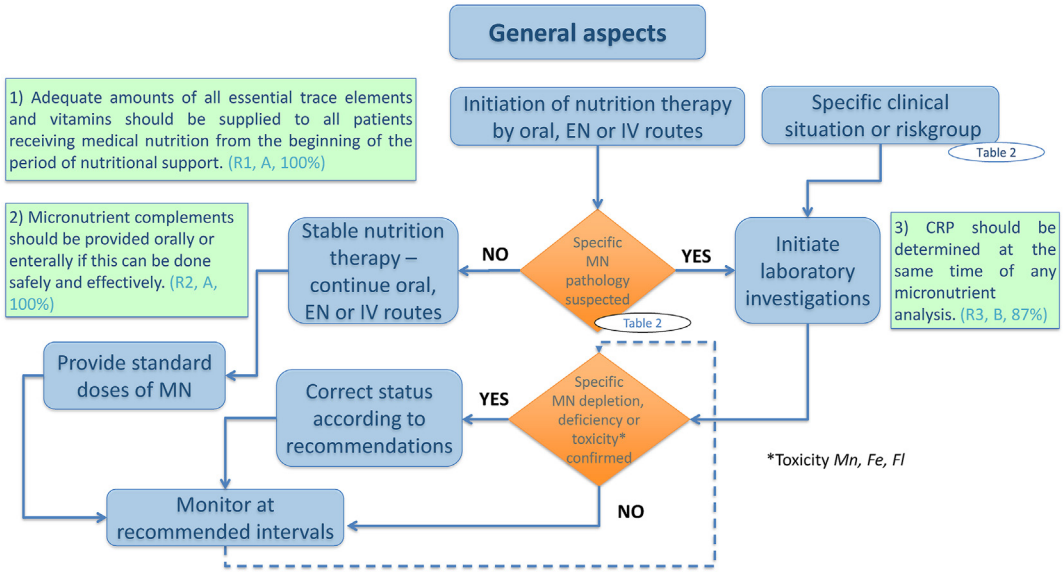

Fig. 2. General strategy for micronutrient handling in clinical practice. Abbreviation: CRP, C-reactive protein; EN, enteral nutrition; MN, micronutrients; IV, intravenous.

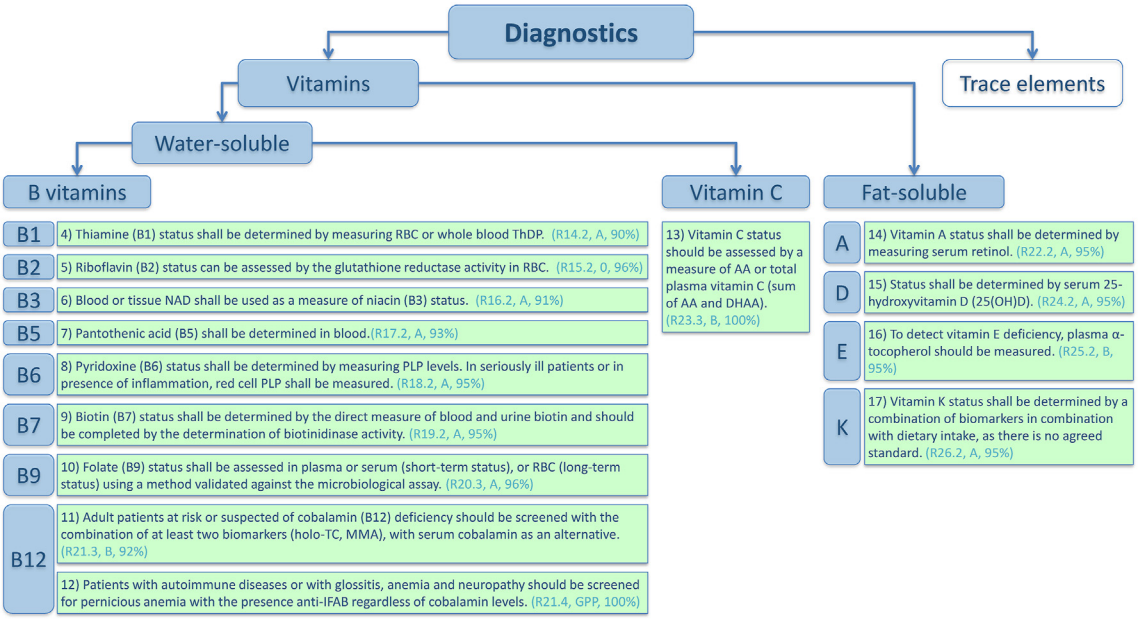

Fig. 3. Diagnostics of vitamins deficiencies. Abbreviations: AA, ascorbic acid; DHA, dehydroascorbic acid; holo-TC, holo-transcobalamin; MMA, methyl malonic acid; NAD, nicotinamid adenine dinucleotide; PLP, pyridoxal phosphate; RBC, red blood cell; ThDP, thiamine diphosphate.

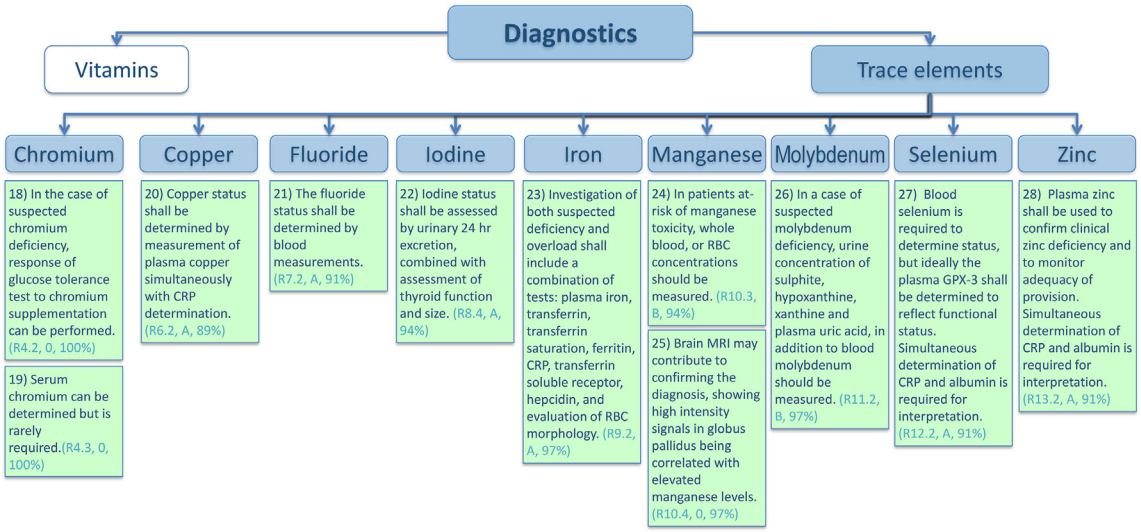

Fig. 4. Diagnosis of trace element disorders. Abbreviations: CRP, C-reactive protein; GPX-3, glutathione peroxidase; PVP-I, povidone iodine; RBC, red blood cell.

and Nutrition Board and the values that are available in clinical settings (Table 1). Whether treating out- or inpatients, there comes a point where MNs need to be prescribed, and a precise wording should be used to characterize it (repletion, complementation, supplementation).

In enteral nutrition (EN), all MN are included in the specific feeding mixtures in a fixed combination, although different commercial preparations may contain different amounts. By choosing a specific enteral product, clinicians can change to some extent the amount of MN provided. The enteral feeding solutions generally deliver all MNs. The ESPEN recommendations are formulated for 1500 kcal/day because this is the most common energy target. But international surveys show that feed delivery is generally below the prescribed target, resulting in lower amounts being frequently delivered [6]. In patients receiving less than 1500 kcal, an additional enteral or intravenous provision of MNs at the start of feeding may be considered, especially if there is a recent history of poor intake [7,8] (Figs. 7–9).

Parenteral nutrition (PN) is different, as the intestine is bypassed, thereby increasing the risk of both insufficiency (absence of MN) and toxicity, if high doses are delivered by the intravenous (IV) route. Follow-up of patients on long-term PN generated knowledge about the minimal doses to deliver to stable patients [9]. The parenteral nutrition patient population is heterogeneous and fixed doses may not fit individual requirements. In numerous non-European countries, many pre-mixed multi-trace element combinations are incomplete, providing only 4 or 6 trace elements, and still contain doses that are not in keeping with the current knowledge, potentially providing inadequate or excessive quantities of different MNs [10]. This report summarizes our recommendations for input during PN and situations where different amounts may be required (Figs. 7–9).

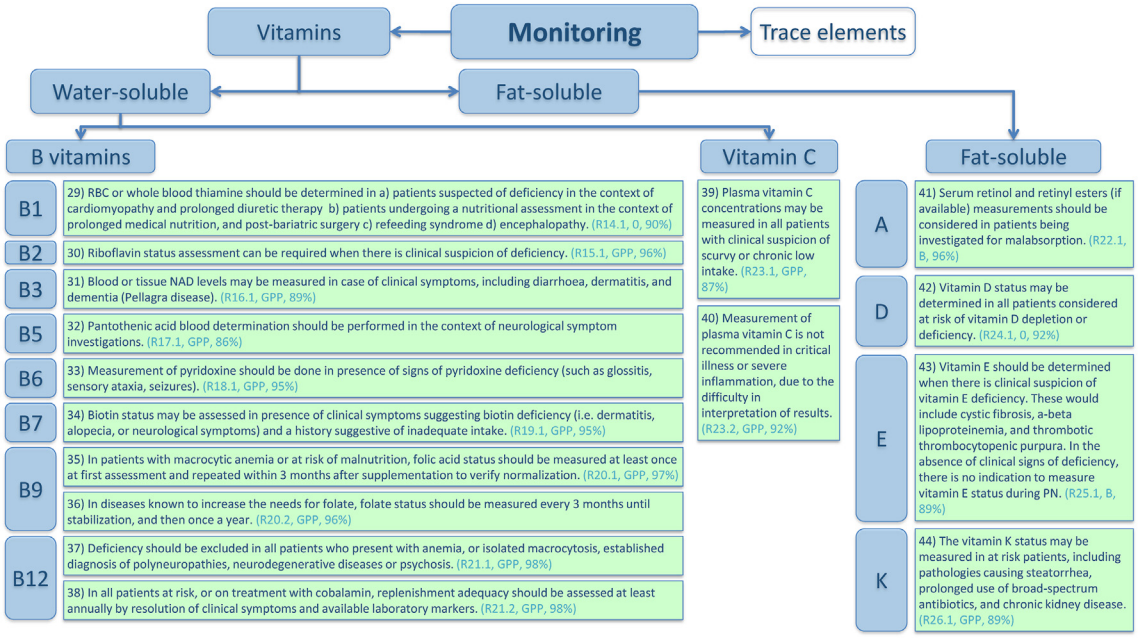

Fig. 5. Monitoring of vitamins. Abbreviations: NAD, nicotinamid adenine dinucleotide; RBC, red blood cell.

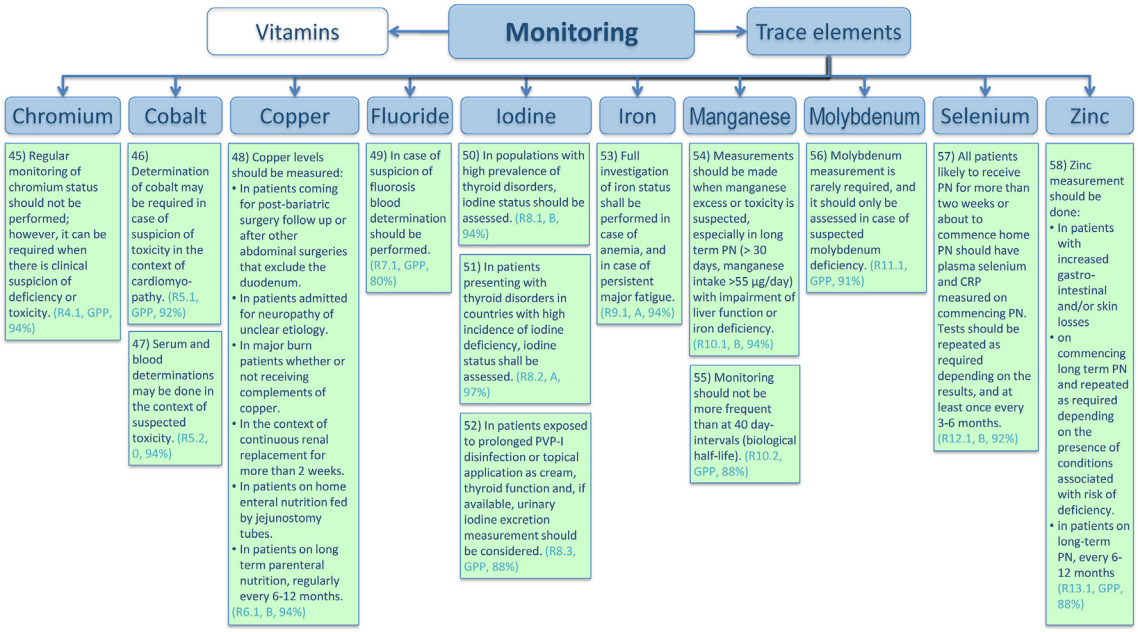

Fig. 6. Monitoring of trace elements. Abbreviations: CRP, C-reactive protein; PVP-I, povidone iodine.

3.2. General comments on provision of micronutrients

Some patients will benefit from "oral nutrition supplements" to complete insufficient oral food intake, whilst not receiving either enteral or parenteral nutrition. Such supplements contain a blend of trace element and/or vitamin preparations, contributing to covering DRI.

An important concept for the water-soluble vitamins is that they have low toxicity and hence most of the recommendations are for a minimal level of supply but increased amounts of all of them would be safe and effective, although possibly wasteful. As summarized in the ASPEN position paper on MN requirements already in 2012 [10], the rationale for providing higher doses than the minimum calculated to be required IV is that many patients have higher vitamin requirements due to malnutrition, baseline deficiencies, and metabolic changes secondary to illness. Moreover, there is likely to be increased excretion of water-soluble vitamins when provided IV. These considerations remain valid a decade later. Hence for some vitamins, the parenteral recommendation is higher than the enteral as shown in Table 2 [1].

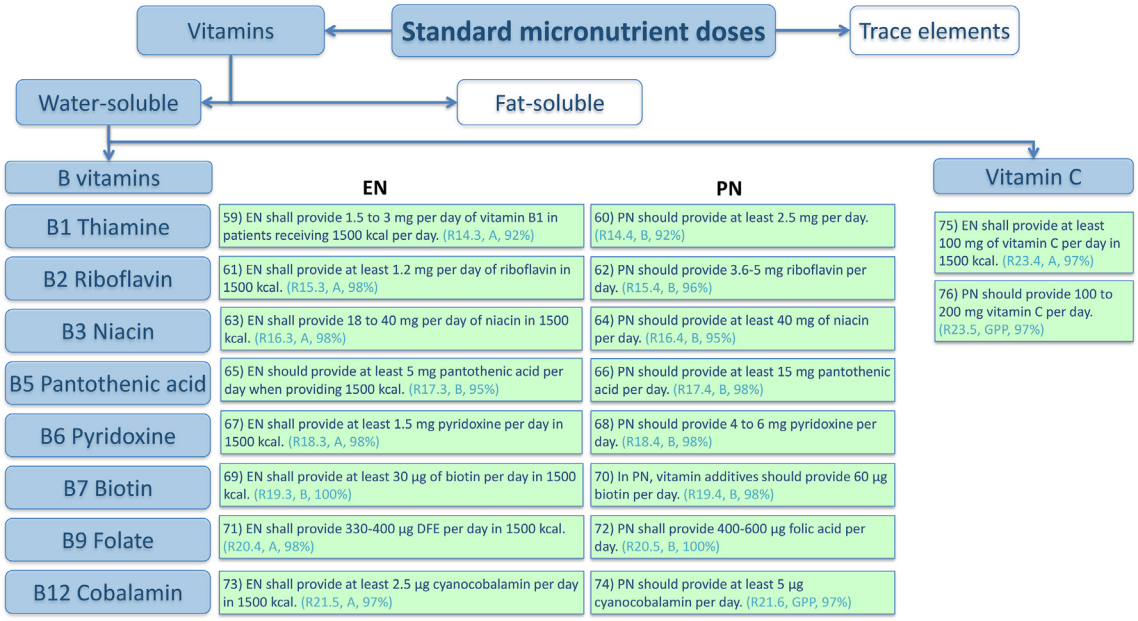

Fig. 7. Standard water-soluble vitamin doses in enteral and parenteral nutrition (for 1500 kcal standard EN and PN). Abbreviation: DFE, dietary folate equivalent.

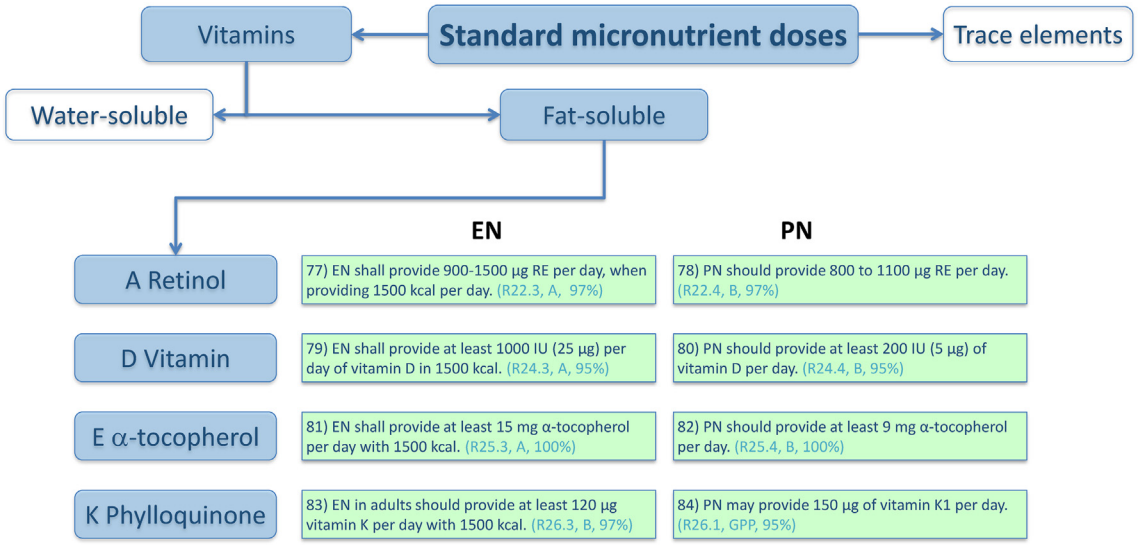

Fig. 8. Standard fat-soluble vitamin doses in enteral and parenteral nutrition (for 1500 kcal standard EN and PN). Abbreviation:RE, retinyl ester.

3.3. *Pathologies at risk*

The present guidelines deliver MN specific recommendations. Nevertheless, for background, the below Table 3 presents a non-exhaustive list of diseases for which specific MNs deficiencies have been demonstrated. This table aims at raising awareness about some often-overlooked aspects of the different diseases, and at considering a combination of MN determinations.

Finally for certain clinical situations the guideline recommends laboratory measuring of blood MN or biomarker concentrations (Figs. 3 and 4). However, this may not be available promptly in all centers which may delay clinical decisions. In such cases, whilst awaiting laboratory results, increasing MN intake, or using a multi-MN preparation, with enhanced clinical monitoring for deficiency symptoms and their resolution upon treatment could be the best option.

Independent of MN specificities, the 3 first general recommendations apply to **all** MN (Fig. 2).

Recommendation 1 (Flowchart N°1)

Adequate amounts of all essential trace elements and vitamins should be supplied to all patients receiving medical nutrition from the beginning of the period of nutritional support.

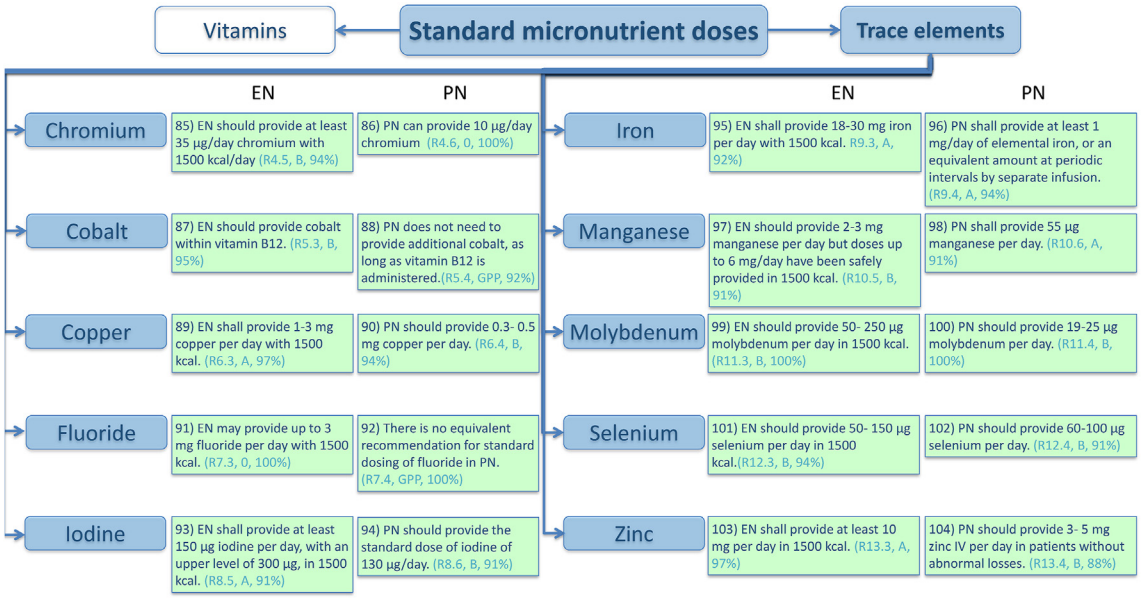

Fig. 9. Standard trace element doses in enteral and parenteral nutrition (for 1500 kcal standard EN and PN). Abbreviation: IV, intravenous.

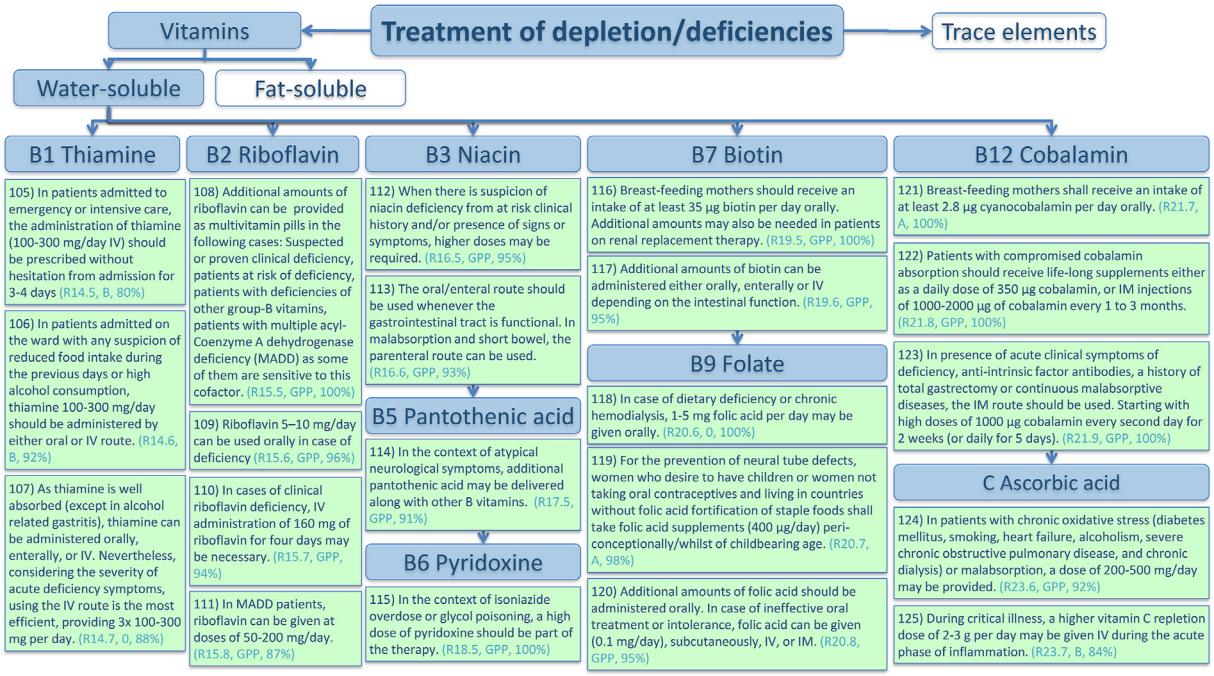

Fig. 10. Treatment guidance of insufficient status of water-soluble vitamins. Abbreviations: IM, intramuscular; IV, intravenous; MADD, multiple acyl-Coenzyme A dehydrogenase deficiency.

Grade of recommendation A – Strong consensus 100 %
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 2 (Flowchart N°2)
Micronutrient complements should be provided orally or enterally if this can be done safely and effectively.

Grade of recommendation A – Strong consensus 100 %
Grade A awarded based on physiology/biochemistry, not clinical trials.

3.4. Impact of inflammation

The presence of inflammation in the context of surgery, trauma, infection or other acute or chronic diseases, complicates the assessment of the status based on blood levels. Using the surrogate biomarker C-reactive protein (CRP) as an indicator of its intensity, it has been clearly shown that inflammation induces a redistribution of many MNs from the circulating compartment to other organs, resulting in low levels for most MNs [2]. Low blood levels therefore do not necessarily indicate deficiency or even depletion. Within

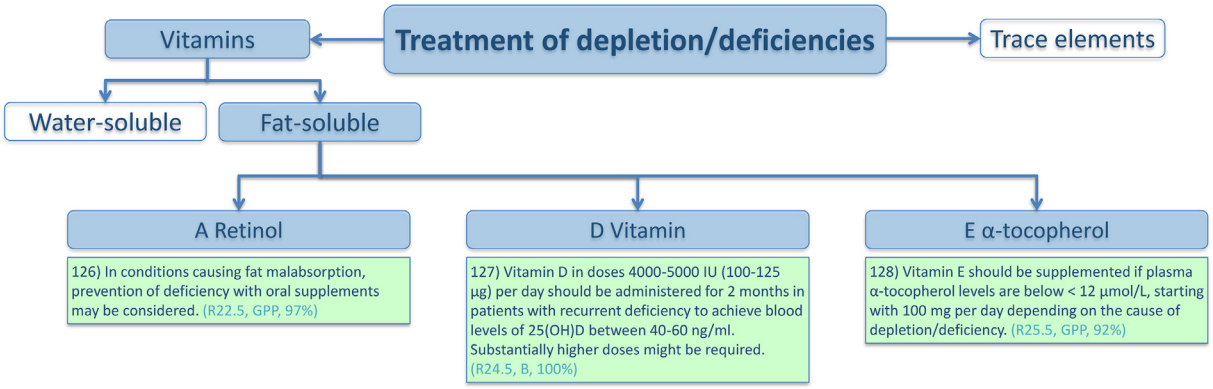

Fig. 11. Treatment of insufficient status of fat-soluble vitamins.

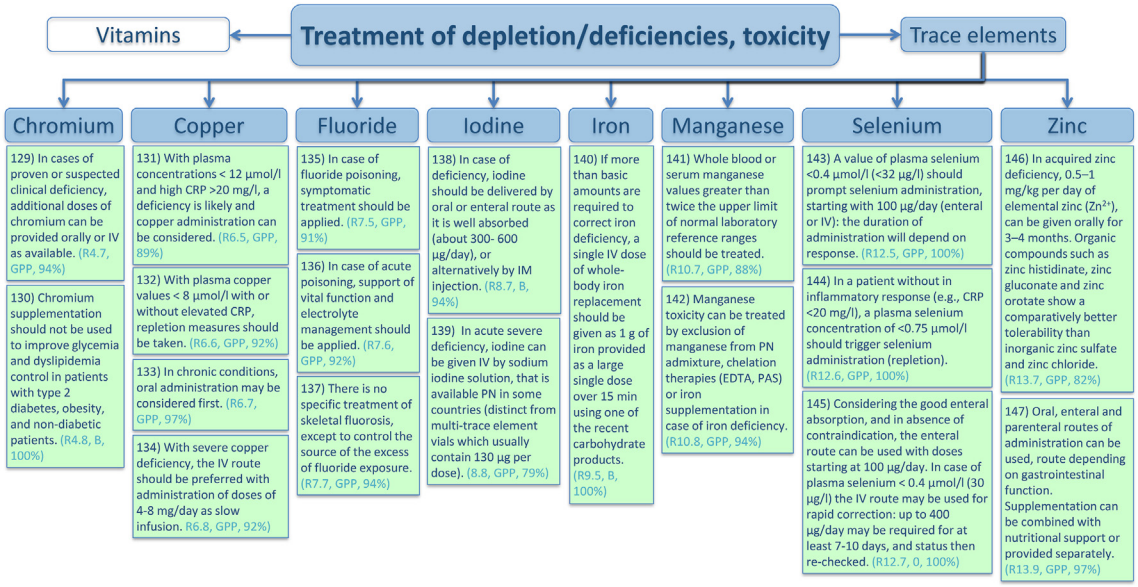

Fig. 12. Treatment guidance including route for insufficient and excess status of trace elements. Abbreviations: CRP, C-reactive protein; IM, intramuscular; IV, intravenous.

24 h of elective surgery in otherwise healthy individuals, plasma concentrations of many trace elements and vitamins have fallen markedly, without any change in whole body MN status [11]. The effects of inflammation in response to acute trauma or infection is usually rapid but may also be prolonged in chronic illness. There are some variations across diseases, and these are discussed with each MN.

Recommendation 3 (Flowchart N° 3)

C-reactive protein should be determined at the same time as any micronutrient analysis.

Grade of recommendation B – Consensus 87 %

Grade A awarded based on physiology, not clinical trials [2,12]

Comment: Single MNs are rarely determined alone. The impact of inflammation usually appears with CRP levels >20 mg/l [3]: therefore high-sensitivity CRP (hs-CRP), which aims at detecting mild inflammation, is not appropriate. Interleukin-6 may be used but is not widely available in clinical settings. Albumin is a carrier protein for many MNs. Its level may be influenced by dilution, and by inflammation, being a negative acute phase protein [11]. Therefore, albumin determination is also desirable whenever MNs are assessed, as it is the carrier of most MNs.

The availability of optimal analytical methods is essential for diagnosis. The recommended methods are provided in the below Table 4 for trace elements, and in Fig. 3 of the flowchart for vitamins.

4. Chromium

Chromium (Cr) exists in several valence states. While Cr IV, V and VI are carcinogenic, the trivalent chromium is the biologically active, stable form. Insufficient intakes are frequent in industrial countries, and are associated with alterations of glucose metabolism, especially in older adults [13]. Also, at risk of deficiency are patients with acute illness due to metabolic stress (burns, trauma, infection), or patients with decreased absorption/intake (short bowel syndrome and PN without chromium supplementation). Chromium deficiency has been reported in adults with chronic intestinal failure after massive bowel resection receiving long-term PN without chromium [14–17]. The clinical manifestations were glucose intolerance, weight loss, elevated plasma free fatty acids and neuropathy that were reversed by

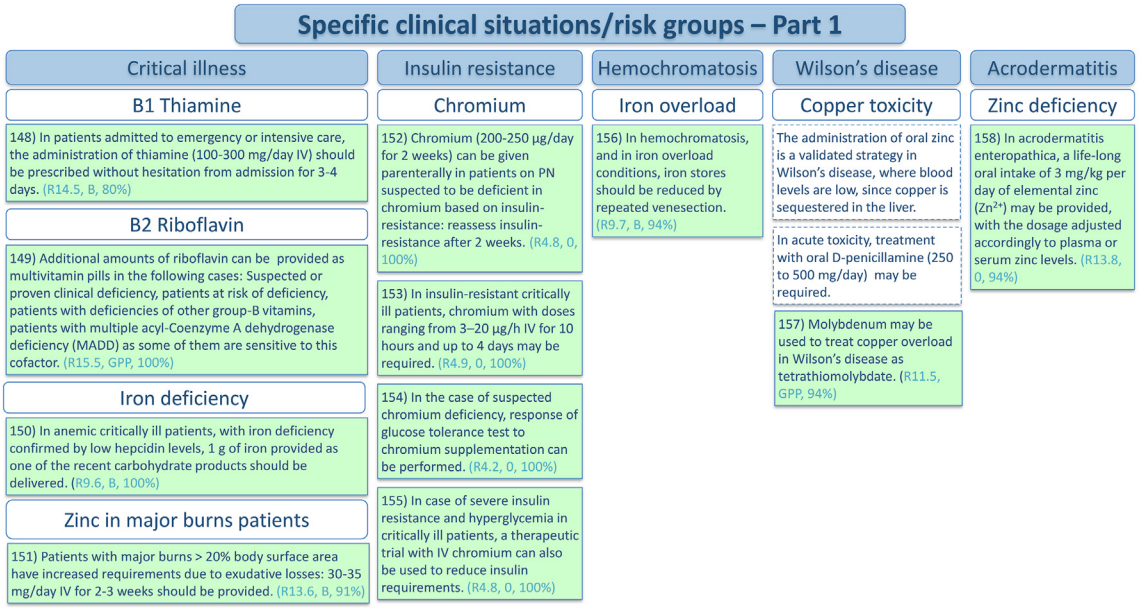

Fig. 13. Measurement and/or treatment guidance for micronutrients in risk groups and in special clinical situations. Recommendations in white boxes have not been formally agreed upon: for further explanation see text). Abbreviations: IV, intravenous; MADD, multiple acyl-Coenzyme A dehydrogenase deficiency.

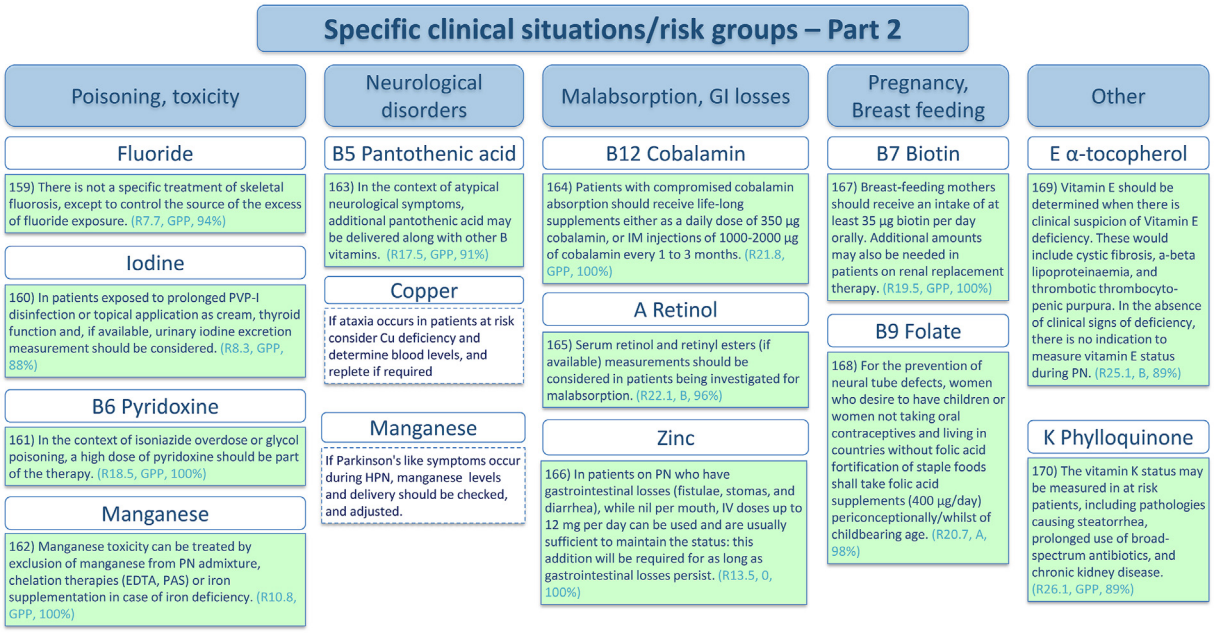

Fig. 14. Measurement and treatment guidance for micronutrients in risk groups and in special clinical situations (recommendations in white boxes have not been formally agreed upon, for further explanation see text).

daily chromium supplementation in the PN solution [18,19]. Chromium insufficiency has been hypothesized to contribute to the development of type 2 diabetes and some studies have revealed a negative relationship between serum chromium and HbA_{1C} levels.

Toxicity depends on the valency: Cr (VI) is carcinogenic, nephrotoxic and causes dermatitis [20]. Both Cr (VI) and Cr (III) are capable of producing ROS (reactive oxygen species) [20]. Ingested trivalent chromium has a low level of toxicity due partially to its poor absorption [14]. Parenteral Cr (III) may have a higher potential toxicity. Data points to a need to lower the recommended amount of parenteral chromium. It has been suggested that it is not necessary to give extra chromium in patients on PN, due to the widespread contamination in PN components [10,14].

4.1. When and what to measure

Recommendation 4.1: Regular monitoring of chromium status should not be performed; however, it can be required when there is clinical suspicion of deficiency or toxicity.

Table 1
Some important definitions and terminology related to assessment, requirements, and prescription of MN.

	ESPEN Definition	Comments
Definition of the words related to assessment of status		
Depletion	Presence of an objective loss of a MN in body fluids, or intake below standard recommendation with blood/plasma concentrations below reference range (see below).	Clinical signs or symptoms are not present at this stage
Deficiency	Evidence of objective loss of a MN in body fluids, or intake below standard recommendation **AND EITHER:** Presence of clinical signs or symptoms, compatible with a micronutrient deficiency **OR** Blood/plasma concentrations below reference range together with metabolic effects of inadequacy	Intake is not meeting losses Depending on the body stores, which vary for each MN, clinical signs of deficiency generally may require many weeks to become visible. Therefore, they are absent in acute conditions, such as intensive care. For example: B1 deficiency can occur in a very short period, whereas B12 deficiency can take months or years to appear
Established terms used to describe micronutrient requirements		
DRI = Dietary reference intake	Set of reference values including EAR, AI, RDA, UL, that, when adhered to, predict a low probability of nutrient inadequacy or excessive intake	DRIs are intended for the general population and will be used to indicate proportions of MNs used particularly in enteral nutrition
PN-DR = PN Daily recommended doses	The doses used in PN are extrapolated from RDAs, bioavailability studies and long-term follow up of patients on home PN. They aim at covering basal needs in most patients. Individual patients may have increased or decreased needs.	The commercially available preparations contain variable amounts of MNs. Growing data indicates that many are outdated providing either too much or too little of particular MNs.
Wording used to describe the type of prescription		
Complement	Complementation will be used to indicate the delivery of micronutrients to cover basal needs (e.g. to complete enteral feeds [8] or PN).	This action is likely to be needed to cover basal needs in case of progressive or insufficient EN
Repletion	Doses aiming to *restore a normal status*, and where the deficit is known. Sometimes called supplementation but term to be avoided as confusing	The term "Repletion" will be used when deficiency or losses are identified or presumed: the administration aims at restoring a normal status.
Supplementation	Term used when the aim is to deliver higher than standard doses (i.e. superior to DRI or parenteral nutrition recommendation) [122]. The term does not include pharmaco-nutrition but designates doses higher than basal requirements delivered in an attempt to correct depletion or deficiency.	This term is often applied without differentiation of amount whenever a MN is prescribed, which leads to confusion

Abbreviations: AI, adequate intake; EAR, estimated average requirement; EN, enteral nutrition; MN, micronutrient; PN, parenteral nutrition; RDA, recommended dietary allowance; UL, tolerable upper intake levels.

Grade or recommendation GPP – Strong consensus 94 % (No. 45)

Comment: Insufficient intakes are frequent in industrial countries, and are associated with alterations of glucose metabolism, especially in older adults [13].

Recommendation 4.2: In the case of suspected chromium deficiency, response of glucose tolerance test to chromium supplementation can be performed.

Grade of recommendation 0 – Strong consensus 100 % (No. 18, No. 154)

References [13,19]

Recommendation 4.3: Serum chromium can be determined but is rarely required.

Grade of recommendation 0 – Strong consensus 100 % (No. 19)

References [13,21–23]

Table 2
Disease-specific risks of depletion or deficiency in trace elements and vitamins.

Disease	Deficiency favouring disease development	Inadequacy or deficit worsening the condition	Deficiency as a result of disease
Alcoholism		B1, Fe	A, D, E, K, B1, B2, B6, B7, B9, B12, C, Zn
Alcoholic hepatitis	B6, Zn	Fe, Zn	
Anaemia	B1, B6, B9, B12, Fe, Cu, Co		
Cancer cachexia	D, Zn		
Cardiomyopathies/Heart failure	B1, B6, D, Se, Fe	Se	
Chronic obstructive pulmonary disease	D, Cu, Se, Mn, Zn		
Chronic intestinal failure			B2, B7, B9, B12, A, D, E, K, Cu, Fe, Zn
Atrophic gastritis			B9, B12, C, D, Fe
Diabetes mellitus	B9, Cr		
Inflammatory bowel diseases		Zn	B1, B6, B12, A, D, E, K, Fe, Se, Zn
Non-alcoholic fatty liver disease	Cu		
Liver diseases		Zn	B12, A, D, E, Se, Zn
Multiple sclerosis	B7		
Obesity	β-carotene, E, Se, Zn	B1, B9, D, Fe, Se, Zn	
Obesity Post Bariatric surgery			A, D, E, K, B1, B9, B12, C, Cu, Zn, Fe
Osteoporosis	B12, D, K, Cu, Fe, Zn, Mn, F, Bo		
Renal failure (chronic)			B1, B6, B9, K, D, Cu, Se, Zn
Sarcopenia	B1, B12, D, Zn, carnitine	D, Se, Zn	
Critical illness		B1, C, D, Cu, Fe, Se, Zn	B1, B12, Cr, D, Fe, Se, Zn

Note: the below list of diseases associated with known alterations of MNs is non-exhaustive (alphabetic order) and may in some cases be less fully supported by the evidence. These and other diseases may have further or still unknown associations with various MN inadequacies. For detailed references see original MN guideline [1].

Table 3
ESPEN Recommendations for daily trace element and vitamin intakes – 2022 (all values are per day).

	PN Home & long-term A	PN high requirements[a] B	EN in 1500 kcal[b] C	EN high requirements in 1500 kcal[c]	DRI per day Age 31->70 years	EC directive[d]: Min-max per 1500 kcal
Trace elements						
Chromium	10–15 μg	15 μg	35–150 μg	200 μg	20–35 μg	18.75–225 μg
Copper	0.3–0.5 mg	0.5–1.0 mg	1–3 mg	Same as C	0.9 mg	0.9–7.5 mg
Fluoride	0–1 mg	Same as A	0–3 mg	3–4 mg	3–5 mg (AI)	0–3 mg
Iodine	130 μg	Same as A	150–300 μg	Same as C	150 μg	97.5–525 μg
Iron	1.0 mg	Same as A	18–30 mg	30 mg	8 mg (18 mg F 19–50 yrs)	7.5–30 mg
Manganese	55 μg	Same as A	2–3 mg	Same as C	1.8–2.3 mg	0.75–7.5 mg
Molybdenum	19–25 μg	Same as A	50–250 μg	250 μg	45 μg	52.5–270 μg
Selenium	60–100 μg	150–200 μg	50–150 μg	200 μg	55 μg	37.5–150 μg
Zinc	3–5 mg	6–12 mg	10–20 mg	20 mg	8–11 mg	7.5–22.5 mg
Lipo-soluble vitamins						
A Retinol[e]	800–1100 μg	1100 μg	900–1500 μg	1500 μg	700–900 μg	525–2700 μg
D3 Cholecalciferol	200 IU/5 μg	800–1000 IU/20–25 μg	25 μg	30 μg	15–20 μg	7,5–37,5 μg
E α-tocopherol	≥9 mg	20–25 mg	15 mg	40 mg	15 mg	7.5–45 mg
K2 menaquinone	150 μg[f]	1–10 mg[g]	120 μg	Same as C	90–120 μg	52.5–300 μg
Water-soluble vitamins	Provide at least[h]		Provide at least[h]			
B1 Thiamine	2.5 mg	100–200 mg	1.5 mg	100 mg	1.1–1.2 mg	0.9–7.5 mg
B2 Riboflavin	3.6 mg	10 mg	1.2 mg	10 mg	1.1–1.3 mg	1.2–7.5 mg
B3 Niacin	40 mg	Same as A	18 mg	40 mg	11–16 mg	13.5–45 mg
B5 Pantothenic acid	15 mg	Same as A	5 mg	7.5 mg	5 mg	2.25–22.5 mg
B6 Pyridoxine	4 mg	6 mg	1.5 mg	7.5 mg	1.5–1.7 mg	1.2–7.5 mg
B7 Biotin	60 μg	Same as A	30 μg	75 μg	30 μg (AI)	11.25–112.5 μg
B9 Folic acid	400 μg	600–1000 μg	330–400 μg DFE	500 μg	400 μg DFE	150–750 μg
B12 Cyancobalamin	5 μg	Same as A	>2.5 μg	7.5 μg	2.4 μg	1.05–10.5 μg
C Ascorbic acid	100–200 mg	200–500 mg	100 mg	200 mg	75–90 mg	33.75–330 mg

Abbreviations: EN = enteral nutrition, FSMP = Foods for Special Medical Purposes, PN = parenteral nutrition, AI = Adequate Intake, DFE = dietary folate equivalent.
[a] : Increased requirements may occur in patients with on-going increased losses such as gastrointestinal losses, continuous renal replacement therapy, those who are hypermetabolic or who are depleted before commencing PN, and in pregnancy.
[b] : The 1500 kcal value has been chosen based on numerous studies confirming that this value seems to be a very common objective. In case of higher nutrient delivery (e.g. 2000 kcal per day or more), exceeding this recommendation is not exposing the patient to any risk considering upper tolerable levels.
[c] : increased requirements during critical illness and in patients with acute admission with malnutrition (NRS ≥5): intended for max 15 days as repletion, to avoid requiring IV supply.
[d] : The EC directive.
[e] : Retinol includes retinol and retinyl ester.
[f] : During PN, vitamin K requirements are usually provided by the lipid emulsions.
[g] : High dose administered in case of coagulopathy (not nutrition-related).
[h] : For water-soluble vitamins, amounts recommended are minimum amounts, and more can usually be safely delivered.

4.2. How much to provide in typical EN and PN

Recommendation 4.4: Enteral nutrition should provide at least 35 μg/day chromium with 1500 kcal/day.

Grade of recommendation B – Strong consensus 94 % (No. 85)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 4.5 Parenteral nutrition can provide at least 10 μg per day

Grade of recommendation 0 – Strong consensus 100 % (No. 86)
References [16,17,24–26]

Comment: the requirement in PN is still debated, especially since absorption of chromium is low, and no trials have been

Table 4
Recommended analytical methods.

Chromium	Chromium status assessment is based on determination of serum and urine levels using ICP-MS. Serum chromium can be determined but is rarely required.
Copper	Several methods are available: the most precise and applicable to biological fluids is ICP-MS, although atomic absorption spectroscopy is also frequently used
Fluoride	Analytical methods use a fluoride-specific electrode (urine), flow injection analysis coupled with a fluoride-specific electrode (serum and urine) (FIA-FE), or by ion chromatography with conductivity detection (IC-CD)
Iodine	Iodine status is best determined by 24 h urine collections. Classically, deficiency diagnosis is based on urinary excretion of iodine <100 μg/24 h. Analytical methods consist in selective electrode (iodide), a chemical method (total iodine) or more recently on ICP-MS. Iodine may also be determined in serum by ICP-MS
Iron	Iron status assessment requires the simultaneous determination of hemoglobin, ferritin (storage form of iron), transferrin saturation and total Iron-binding capacity, and occasionally bone marrow iron staining. The most recent methods include the determinations of hepcidin, zinc protoporphyrin, and soluble transferrin receptor
Manganese	Manganese status is best assessed by whole blood or RBC concentration measured by ICP-MS or atomic absorption spectroscopy. Plasma or serum concentration can also be measured
Molybdenum	Molybdenum can be determined in blood, urine or hair by ICP-MS, and also by neutron activation analysis
Selenium	Selenium status is most commonly obtained from plasma or whole blood selenium measurement by CFAAS or ICP-MS. Selenoprotein P and plasma glutathione peroxidase (GPX3) are more accurate measures of whole-body status
Zinc	Total zinc can be measured in whole blood, plasma, serum, urine, or hair preferably by ICP-MS, or by atomic absorption spectroscopy

Abbreviations: CFAAS, carbon furnace atomic absorption spectrometry; FIA-FE, flow injection analysis coupled with a fluoride-specific electrode; GPX3, glutathione peroxidase; IC-CD, ion chromatography with conductivity detection; ICP-MS, inductively coupled plasma mass spectrometry; RBC, red blood cell.

performed with lower doses. The above doses have been used safely and effectively in adults for many years. More research on chromium is required.

4.3. When and how to provide additional amounts

Recommendation 4.6: In cases of proven or suspected clinical deficiency, additional doses of chromium can be provided orally or IV as available.

Grade of recommendation GPP – Strong consensus 94 % (No. 129)

Recommendation 4.7: Chromium supplementation should not be used to improve glycemia and dyslipidemia control in patients with type 2 diabetes, obesity, and non-diabetic patients.

Grade of recommendation B – Strong consensus 100 % (No. 130)
References [18,27–31]

Recommendation 4.8: In case of severe insulin resistance and hyperglycemia in critically ill patients, a therapeutic trial with IV chromium can also be used to reduce insulin requirements.

Grade of recommendation 0 – Strong consensus 100 % (No. 155)
References [21–23]

Comment: A low plasma chromium level is associated with hyperglycemia, insulin resistance, high inflammatory status and increased cardiovascular risk in humans [18,19]. These recommendations are not applicable to general diabetic patients, but only for critically ill patients, in case of increasing insulin doses (30–50 U/hour of insulin required to maintain blood glucose <10 mmol/l). Such a trial is limited to 4 days [21–23].

Recommendation 4.9: Chromium (200–250 μg/day for 2 weeks) can be given parenterally in patients on parenteral nutrition suspected to be deficient in chromium based on insulin-resistance: reassess insulin-resistance after 2 weeks.

Grade of recommendation 0 – Strong consensus 91 % (No. 152)
References [21–23].

Recommendation 4.10: In insulin-resistant critically ill patients, chromium with doses ranging from 3 to 20 μg/h IV for 10 h and up to 4 days may be required.

Grade of recommendation 0 – Strong consensus 100 % (No. 153)
References [21–23].

5. Cobalt

Cobalt is a rare element with properties like iron and nickel. It is essential for the formation of vitamin B12 [32]. All the essential functions of cobalt are covered in the chapter about vitamin B12.

5.1. When and what to measure

Recommendation 5.1: Determination of cobalt may be required in case of suspicion of toxicity in the context of cardiomyopathy.

Grade or recommendation GPP – Strong consensus 92 % (No. 46)

Recommendation 5.2: Serum and blood determinations may be done in the context of suspected toxicity.

Grade of recommendation 0 – Strong consensus 94 % (No. 47)
Grade 0 awarded based on biochemistry, not clinical trials [32]

Comment: Human beings may be exposed to cobalt through occupational contact (glass, inks, and paints), in processing plants, hard-metal industry, diamond polishing, and the manufacture of ceramics. In cases of suspected cobalt toxicity, the assessment of the status is based on determination of serum [33] and urine levels [34,35] using inductively coupled plasma mass spectrometry (ICP-MS).

5.2. How much to provide in typical EN and PN

Recommendation 5.3: Enteral nutrition should provide cobalt within vitamin B12.

Grade of recommendation B– Strong consensus 95 % (No. 87)
Grade B awarded based on physiology/biochemistry (no DRI), not clinical trials [36,37],

Recommendation 5.4: Parenteral nutrition does not need to provide additional cobalt, as long as vitamin B12 is administered.

Grade of recommendation GPP – Strong consensus 92 % (No. 88)

6. Copper

Copper exists in two different redox states: the oxidized cupric (Cu^{2+}) and reduced cuprous (Cu^{+}) forms. It serves as an essential catalytic cofactor in redox chemistry for proteins involved in growth and development [38], and as an essential cofactor for oxidation–reduction reactions involving copper-containing oxidases. Absorption occurs in the stomach and small intestine, primarily in the duodenum [39], and is highly regulated.

Copper depletion is observed in some acute conditions such as major burns, after gastric and bariatric surgery, and in patients requiring continuous renal replacement therapy, or in prolonged PN or EN without adequate copper [40–46]. Symptoms of deficiency require some weeks to develop and are not readily recognized. The acute symptoms include cardiac arrhythmias, myeloneuropathy, and delayed wound healing [45,47]. The chronic symptoms include microcytic anemia, neutropenia, osteoporosis, ataxia, and hair de-pigmentation [47].

Supra-normal blood levels are observed in inflammatory conditions, reflecting the increase in ceruloplasmin. Elevated copper levels exist in Alzheimer's disease [48], and are observed in pathologies such as infections, hemopathies, haemochromatosis, hyperthyroidism, liver cirrhosis and hepatitis, and physiologically, in pregnancy.

Intoxication is rare but may occur in an industrial context. Cholestasis can also affect the liver's ability to excrete copper, resulting in chronic copper toxicity [49]. It is also increased in genetic disorders such as Wilson's disease, and in Menke's syndrome [49]. Toxicity symptoms include hematemesis, hypotension, melena (black “tarry” feces), coma, headaches, behavioral changes, fever, diarrhea, abdominal cramps, brown ring-shaped markings in eyes (Kayser-Fleischer rings), and jaundice. Not included as a recommendation in the 2022 guideline, but considering its importance we include in Fig. 13 for completeness the first line therapy of Wilson's disease with hepatic neurological and symptoms, which is penicillamine and zinc salts [50]:

tetrathiomolybdate (R11.5) is a strong decoppering agent but remains an experimental therapy, as clinical experience is limited.

6.1. When and what to measure

Recommendation 6.1: Copper levels should be measured:

- In patients coming for post-bariatric surgery follow up or after other abdominal surgeries that exclude the duodenum.
- In patients admitted for neuropathy of unclear etiology.
- In major burn patients whether receiving, or not, complements of copper.
- In the context of continuous renal replacement for more than 2 weeks.
- In patients on home enteral nutrition fed by jejunostomy tubes.
- In patients on long term parenteral nutrition, regularly every 6–12 months.

Grade of recommendation B – Strong consensus 94 % (No. 48)
References [41,46,51–54]

Comment: If ataxia occurs in patients at risk (see R6.1), copper deficiency should be considered with determination of blood levels, followed by repletion if confirmed. The increasing number of reports of neurological symptoms after bariatric surgery made it important to insert it among MN related neurological disorders (Fig. 13).

Recommendation 6.2: Copper status shall be determined by measurement of plasma copper simultaneously with CRP determination.

Grade of recommendation A – Consensus 89 % (No. 20)
Grade A awarded based on biochemistry, not clinical trials.

Comment: Copper, a long-ignored trace element, is an essential catalytic cofactor in redox chemistry for proteins involved in growth and development [55], and as an essential cofactor for oxidation–reduction reactions involving copper-containing oxidases. Copper concentrations in plasma increase in the context of an inflammatory response since ceruloplasmin is a positive acute phase reactant [2]. A normal serum copper in the presence of an elevated CRP would suggest copper depletion or deficiency. In case of uncertainty, ceruloplasmin concentrations will assist diagnosis, as low values of the latter provide confirmation of deficiency.

6.2. How much to provide in typical EN and PN

Recommendation 6.3: Enteral nutrition shall provide 1–3 mg copper per day with 1500 kcal.

Grade of recommendation A – Strong consensus 97 % (No. 89)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 6.4: Parenteral nutrition should provide 0.3–0.5 mg copper per day.

Grade of recommendation B – Strong consensus 94 % respectively (No. 90)
Recommendations [42,43,56]

6.3. When and how to provide additional amounts

Recommendation 6.5: With plasma concentrations <12 μmol/l and high CRP >20 mg/l, a deficiency is likely and copper administration can be considered.

Grade of recommendation GPP – Consensus 89 % (No. 131)

Recommendation 6.6: With plasma copper values < 8 μmol/l with or without elevated CRP, repletion measures should be taken.

Grade of recommendation GPP – Strong consensus 97 % (No. 132)

Recommendation 6.7: In chronic conditions, oral administration may be considered first.

Grade of recommendation GPP – Strong consensus 94 % (No. 133)

Recommendation 6.8: With severe copper deficiency, the IV route should be preferred with administration of doses of 4–8 mg/day as slow infusion.

Grade of recommendation GPP – Strong consensus 92 % (No. 134)

7. Fluoride

Fluoride is an abundant element [57], occurring in soils, rocks, and water: it is therefore naturally present in the food and drink we consume. Its status as “essential” is debated. Reported unequivocal signs of fluoride deficiency are almost non-existent. Pharmacological doses prevent caries.

Chronic toxicity is most frequent, and may present as gastric complaints, anemia, osteomalacia, teeth problems, and neuromuscular and gastrointestinal symptoms. Chronic toxicity has been observed along with excessive water supplies and industrial exposures (excess of 2 mg/day) resulting in dental fluorosis and mottled enamel. Skeletal fluorosis is a rare toxic osteopathy characterized by massive bone fluoride fixation that occurs with doses 10–25 mg/day for many years. The disease is an endemic problem in some parts of the world [58,59]. In patients on home PN for chronic intestinal failure, high blood fluoride values due to high fluoride intakes from drinking water have been reported [60].

7.1. When and what to measure

Recommendation 7.1: In case of suspicion of fluorosis blood determination should be performed.

Grade of recommendation GPP – Consensus 88 % (No. 49)

Recommendation 7.2: The fluoride status shall be determined by blood measurements.

Grade of recommendation A – Strong consensus 91 % (No. 21)
Grade A awarded based on biochemistry, not clinical trials.

7.2. How much to provide in typical EN and PN

Recommendations 7.3: Enteral nutrition may provide up to 3 mg fluoride per day with 1500 kcal.

Grade of recommendation 0– Strong consensus 100 % (No. 91)
Grade 0 awarded based on DRI/RDA, not clinical trials (absence of DRI).

Recommendations 7.4: There is no equivalent recommendation for standard dosing of fluoride in parenteral nutrition.

Grade of recommendation GPP – Strong consensus 100 % (No. 92)

Comment: There is no DRI. Fluoride is not essential in children nor in adults. Adults typically consume <0.5 mg of fluoride daily in food [61]. Nutritional intakes in adults are safe up to 4 mg/day in men and 3 mg/day in women. Although not essential in adult PN, 0.95 mg per day has been provided without any complication and may be continued. It is not provided in North America.

7.3. When and how to treat

Recommendation 7.5: In case of fluoride poisoning, symptomatic treatment should be applied.

Grade of recommendation GPP – Strong consensus 91 % (No. 135)

Recommendation 7.6: In case of acute poisoning, support of vital function and electrolyte management should be applied.

Grade of recommendation GPP – Strong consensus 97 % (No. 136)

Recommendation 7.7: There is not a specific treatment of skeletal fluorosis, except to control the source of the excess of fluoride exposure.

Grade of recommendation GPP Strong consensus 94 % (No. 137)

8. Iodine

Iodine plays a central role in thyroid physiology, being both a major constituent of thyroid hormones and a regulator of thyroid gland function. Importantly, healthy thyroid function depends also on an adequate provision of selenium (liver deiodination) and iron (metabolism) at any age.

Iodine deficiency disorders represent a global health threat to individuals and societies, including affluent countries in Europe, and impose a significant burden on public healthcare systems. Severe iodine deficiency causes goiter and hypothyroidism [62]. Iodine deficiency increases the risk of developing autonomous thyroid nodules that are unresponsive to TSH control [63].

Moreover, iodine deficiency during pregnancy and breastfeeding adversely affects the development of the child [64,65]. Even mild or moderate iodine deficiency in the mother affects the synthesis of thyroid hormones and may impair brain development. During pregnancy, women have a sharply increased need for iodine, which is frequently not covered by food sources and iodine supplements. Patients on long-term PN may be at risk of deficiency [66].

8.1. When and what to measure

Recommendation 8.1: In populations with high prevalence of thyroid disorders, iodine status should be assessed.

Grade of recommendation B – Strong consensus 94 % (No. 50)
Reference [67]

Recommendation 8.2: In patients presenting with thyroid disorders in countries with high incidence of iodine deficiency, iodine status shall be assessed.

Grade of recommendation A – Strong consensus 97 % (No. 51)
References [67–70]

Recommendation 8.3: In patients exposed to prolonged povidone iodine (PVP–I) disinfection or topical application as cream, thyroid function and, if available, urinary iodine excretion measurement should be considered.

Grade of recommendation GPP - Consensus 88 % (No. 52, No. 160)

Recommendation 8.4: Iodine status shall be assessed by urinary 24-h excretion, combined with assessment of thyroid function and size.

Grade of recommendation A – Strong consensus 94 % (No. 22)
Grade A awarded based on biochemistry, not clinical trials.

Comment: Iodine deficiency is a persistent public health problem in Europe [71] and in the World. Classically, deficiency diagnosis is based on urinary excretion of iodine <100μg/24 h: the measurement is not usually available in hospitals. Iodine status evaluation can be considered in patients with hyperthyroidism or hypothyroidism and prolonged topical iodine exposure after having excluded other etiological factors. Serum thyroid stimulating hormone (TSH) is not a sensitive indicator of iodine status whether in children or adults, as concentrations are usually maintained within a normal range despite frank iodine deficiency [63].

8.2. How much to provide in typical EN and PN

Recommendation 8.5: Enteral nutrition shall provide at least 150 μg iodine per day, with an upper level of 300 μg, in 1500 kcal.

Grade of recommendation A – Strong consensus 91 % (No. 92)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 8.6: Parenteral nutrition should provide the standard dose of 130 μg/day.

Grade of recommendation B – Strong consensus 91 % (No. 93)
References [52,66–68,72]

8.3. How to provide additional amounts

Recommendation 8.7: In case of deficiency, iodine should be delivered by oral or enteral route as it is well absorbed (about 300–600 μg/day), or alternatively by IM injection.

Grade of recommendation B – Strong consensus 94 % (No. 138)
Reference [73]

Recommendation 8.8: In acute severe deficiency, iodide can be given IV by sodium iodide solution, that is available for parenteral nutrition in some countries (distinct from multi-trace element vials which usually contain 130 μg per dose).

Grade of recommendation GPP – Consensus 79 % (No. 139)

9. Iron

Iron (Fe) is the most abundant trace element in the human body. The two most common iron states are the divalent ferrous (Fe^{2+}) and the trivalent ferric (Fe^{3+}). It is required for most, if not all, pathways for energy and substrate metabolism [74]. The main

function of iron is as a functional component of heme, participating in oxygen binding and transport (hemoglobin, myoglobin), oxygen metabolism (catalases, peroxidases), cellular respiration and electron transport (cytochromes) [74–76].

Worldwide, iron deficiency is the most common nutritional deficiency, affecting hundreds of millions of people [77,78]. It has economic consequences as it reduces working capacity, increasing sick leave, and being often incorrectly treated [79].

Iron depletion and deficiency progresses through several stages [80,81]. Storage depletion is characterized by decreasing serum ferritin concentrations and levels of iron in bone marrow. In Marginal deficiency, iron stores are depleted, iron supply to erythropoietic cells and transferrin saturation are reduced, but hemoglobin parameters remain within the normal range. When iron deficiency anemia develops, the stores are exhausted; hematocrit and levels of hemoglobin decline; and the resulting microcytic, hypochromic anemia is characterized by small RBC [79].

Iron overload: The most common causes are hereditary hemochromatosis *(HFE*-associated), and other rare genetic disorders, but it may develop secondary to transfusion (Thalassemia, etc). The signs and symptoms of overload are non-specific [82], and include chronic fatigue, joint pain, and diabetes: the disorder evolves towards end-organ failure, involving particularly the pancreas and liver [83].

9.1. When and what to measure

Recommendation 9.1: Full investigation of iron status shall be performed in case of anemia, and in case of persistent major fatigue.

Grade of recommendation A – Strong consensus 94 % (No. 53)
References [78–81]

Recommendation 9.2: Investigation of both suspected deficiency and overload shall include a combination of tests: plasma iron, transferrin, transferrin saturation, ferritin, CRP, transferrin soluble receptor, hepcidin, and evaluation of red blood cell (RBC) morphology.

Grade of recommendation A – Strong consensus 97 % (No. 23)
Grade A awarded based on biochemistry, not clinical trials.

9.2. How much to provide in typical EN and PN

Recommendation 9.3: Enteral nutrition shall provide 18–30 mg iron per day with 1500 kcal.

Grade of recommendation A – Strong consensus 94 % (No. 95)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 9.4: Parenteral nutrition shall provide at least 1 mg/day of elemental iron, or an equivalent amount at periodic intervals by separate infusion.

Grade of recommendation A– Strong consensus 92 % (No. 96)
References [84–86].

Comment: This recommendation is high for men and postmenopausal women, but the modestly higher doses provided are likely to be beneficial and not harmful considering the high prevalence of iron deficiency. While nutritional doses shall be provided to any patients whatever the inflammatory status, additional iron high-dose supplementation to correct deficiency during infections and hemato-oncologic disease has been associated with a 1.16 RR of infection [87]: this risk shall be balanced against the consequences of deficiency. If countries do not have iron containing multi-trace element products the above alternative should apply. In patients with low body weight (<40 kg), the 1 mg per day dose should be adapted.

9.3. When and how to provide additional amounts

Recommendation 9.5: If more than basic amounts are required to correct iron deficiency, a single IV dose of whole-body iron replacement should be given as 1 g of iron provided as a large single dose over 15 min using one of the recent carbohydrate products.

Grade of recommendation B – Strong consensus 100 % (No. 140)
References [88,89]

Comment: When IV iron is required, risk minimization should be addressed: anaphylactoid reactions during iron infusions are rare (<1:250,000 administrations with recent formulation) but may be life threatening [90,91]. There are many forms of iron suitable for IV use. Iron sucrose and ferric gluconate are widely used but may require multiple administration. As iron is strongly bound to carbohydrates (carboxymaltose, ferumoxytol, isomaltoside, gluconate, sucrose, low molecular weight iron dextran), the amount of labile iron is low, allowing the rapid administration of large single doses [89,91–94]. The risk is highest with high molecular weight iron dextran. The best studied example is ferric carboxymaltose, infused over 15 min [88,95].

Recommendation 9.6: In anemic critically ill patients, with iron deficiency confirmed by low hepcidin levels, 1 g of iron provided as one of the recent carbohydrate products should be delivered.

Grade of recommendation B – Strong consensus 100 % (No. 150)
References [92–94,96]

Comment: considering the above-mentioned relative risk of infection, such repletion should be undertaken when inflammation abates, and patient is close to discharge.

9.4. When to provide reduced amounts

Recommendation 9.7: In hemochromatosis, and in iron overload conditions, iron stores should be reduced by repeated venesection.

Grade of recommendation B – Strong consensus 94 % (No. 156)
References [97,98]

10. Manganese

Manganese (Mn) is one of the most common metals in the human body, mainly present in the bone, liver, kidney, pancreas, and adrenal and pituitary glands [99]. Manganese is important for many physiological processes such as regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, blood coagulation, and hemostasis, antioxidant defense, and proper immune function [100].

Toxicity is a greater concern than deficiency. The most common somatic effects are hypertension, increased heart rate due to blocking of calcium channels by manganese, and elevated cholesterol levels because of the reduced conversion of cholesterol to bile acids. Other symptoms are decreased fertility in men as well as increased fetal abnormalities [101]. Nevertheless, the

brain is the main target organ of manganese toxicity. Manganese overexposure results in compromised mitochondrial function, oxidative stress, protein misfolding and trafficking, and neuroinflammation [102]. Neurological damage might be irreversible. In patients exposed to manganese, elevated whole-blood manganese has been shown to correlate with MRI signal intensity in globus pallidus. Manganese overload initially induces non-specific symptoms such as headache, asthenia, irritability, fatigue, and muscular pains, but later, a neurodegenerative syndrome with psychiatric symptoms, known as manganism. This condition is like the cognitive, motor, and emotional defects seen in Parkinson's disease. Considering the importance of checking undue Mn delivery, this problem has been included in Fig. 14, despite not being a formal recommendation.

10.1. When and what to measure

Recommendation 10.1: Measurements should be made when manganese excess or toxicity is suspected, especially in long term parenteral nutrition (>30 days, manganese intake >55 μg/day) with impairment of liver function or iron deficiency.

Grade of recommendation B – Strong consensus 94 % (No. 54)
References [103,104]

Recommendation 10.2: Monitoring should not be more frequent than at 40 day-intervals (biological half-life).

Grade of recommendation GPP – Consensus 88 % (No. 55)

Recommendation 10.3: In patients at-risk of manganese toxicity, whole blood, or RBC concentrations should be measured.

Grade of recommendation B – Strong consensus 94 % (No. 24)
Grade B awarded based on biochemistry, not clinical trials [103–105]

Recommendation 10.4: Brain magnetic resonance imaging (MRI) may contribute to confirming the diagnosis, showing high intensity signals in globus pallidus being correlated with elevated manganese levels.

Grade of recommendation 0 – Strong consensus 97 % (No. 25)
References [103,106]

10.2. How much to provide in typical EN and PN

Recommendation 10.5: Enteral nutrition should provide 2–3 mg manganese per day but doses up to 6 mg/day have been safely provided in 1500 kcal.

Grade of recommendation B - Strong consensus 91 % (No. 97)
Reference [7]

Recommendation 10.6: Parenteral nutrition shall provide 55 μg manganese per day.

Grade of recommendation A - Strong consensus 91 % (No. 98)
Reference [104]

Comment: The above recommended dose of Mn in adults treated with PN, are still frequently exceeded by the current multi-trace element products [107]

10.3. When and how to treat?

Recommendation 10.7: Whole blood or serum manganese values greater than twice the upper limit of normal laboratory reference ranges should be treated.

Grade of recommendation GPP - Consensus 88 % (No. 141)

Comments: Dietary intake does not lead to toxicity, because absorption is tightly regulated in the gut [99]. Toxicity has been observed in adults receiving IV > 500 μg/day and in pediatric patients receiving >40 μg/kg/day [102], but even as little as 110 μg/day to adults causes an elevation in whole blood manganese concentration [104]. Patients suffering from cholestasis, liver failure or hepatic encephalopathy can develop manganese toxicity, as manganese is excreted in the bile [103,108]. Due to neuronal cell death in basal ganglia structures, functional recovery, and effective treatment for manganism is currently limited [108].

Recommendation 10.8: Manganese toxicity can be treated by exclusion of manganese from PN admixture, chelation therapies (EDTA, PAS) or iron supplementation in case of iron deficiency.

Grade of recommendation GPP – Strong consensus 94 % (No. 142, No. 162)

11. Molybdenum

Molybdenum (Mo) is an essential trace element for enzymes of microorganisms, plants and animals. It is used in plants and mammals in amino acid and purine metabolism [109,110]

Clinically apparent nutritional deficiency induced by low dietary molybdenum has not been reported in humans [109]. Molybdenum deficiency may occur in long-term PN without added molybdenum. Deficiency leads to biochemically detectable high plasma methionine, low serum uric acid, and high urinary thiosulfate, xanthine and hypoxanthine [110].

There are no reports of acute toxicity of dietary molybdenum in humans. A controlled study in healthy young men found that molybdenum intakes, ranging from 22 μg/day to 1490 μg/day (almost 1.5 mg/day), elicited no serious adverse effects when molybdenum was given for 24 days [111]. A high concentration of molybdenum may act as an inhibitor in purine catabolism [112], and has been shown to cause copper deficiency in animals.

11.1. When and what to measure

Recommendation 11.1: Molybdenum measurement is rarely required, and it should only be assessed in case of suspected molybdenum deficiency.

Grade of recommendation GPP – Strong consensus 91 % (No. 56)

Recommendation 11.2: In a case of suspected molybdenum deficiency, urine concentration of sulphite, hypoxanthine, xanthine and plasma uric acid, in addition to blood molybdenum should be measured.

Grade of recommendation B – Strong consensus 97 % (No. 26)
Grade A awarded based on biochemistry, not clinical trials

11.2. How much to provide in typical EN and PN

Recommendation 11.3: Enteral nutrition should provide 50–250 μg Molybdenum per day in 1500 kcal.

Grade of recommendation B – Strong consensus 100 % (No. 99)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 11.4: Parenteral nutrition should provide 19–25 μg molybdenum per day.

Grade of recommendation B – Strong consensus 100 % (No. 100)
Reference [113]

11.3. When to provide additional amounts

Recommendation 11.5: Molybdenum may be used to treat copper overload in Wilson's disease as tetrathiomolybdate.

Grade of recommendation GPP – Strong consensus 94 % (No. 157)

12. Selenium

Selenium (Se) is essential in mammals, being required for the synthesis of the amino acid selenocysteine, an essential component of at least 25 selenoproteins in human tissues [114]. The biochemical functions include antioxidant and redox activity, control of thyroid hormone metabolism, together with several proteins of uncertain function [115]. Selenium is well absorbed (56–81 %).

Deficiency is most often caused by insufficient intake, and is largely geography dependent (soil content is highly variable), and may lead to population deficiency and specific chronic pathologies such as the Keshan cardiomyopathy, and Kashin-Beck osteochondropathy in China [116]. Selenium deficiency is associated with increased incidence and virulence of viral infections [117,118]. Milder selenium depletion will cause effects on metabolism and tissue function [115].

Severe deficiency has been recognized during PN as cardiac and skeletal muscle myopathy, and as skin and nail effects [119]. A value of plasma selenium <0.4 μmol/l (<32 μg/l), should always trigger supplements provision, and other actions should be tailored to the combined data from plasma selenium and CRP [119], as inflammation causes a proportional decrease in plasma levels due to redistribution [2,120].

Upper limits for plasma selenium before toxicity symptoms occur are not clear, and range from ≅6 μmol/l [121] to ≅12 μmol/l [122]. Selenium toxicity outbreaks have occurred due to misformulation of dietary supplements resulting in clinical signs of selenosis [123]. The concern comes from recent awareness that selenium overexposure is positively associated with type 2 diabetes and high-grade prostate cancer.

12.1. When and what to measure

Recommendation 12.1: All patients likely to receive PN for more than two weeks or about to commence home PN should have plasma selenium and CRP measured on commencing PN. Tests should be repeated as required depending on the results, and at least once every 3–6 months.

Grade of recommendation B – Strong consensus 92 % (No. 57)
Reference [124]

Recommendation 12.2: Blood selenium is required to determine status, but ideally the plasma glutathione peroxidase (GPX-3) shall be determined to reflect functional status. Simultaneous determination of CRP and albumin is required for interpretation.

Grade of recommendation A – Strong consensus 91 % (No. 27)
Reference [125].

Comment: In many patients there is an element of inflammation. This leads to a reduction in plasma selenium [2], related to redistribution out of the circulating compartment since plasma selenium returns to normal in many cases without supplementation [120]. Selenoprotein P has been shown to be a more selective indicator of status [126].

12.2. How much to provide in typical EN and PN

Recommendation 12.3: Enteral nutrition should provide 50–150 μg selenium per day in 1500 kcal.

Grade of recommendation B – Strong consensus 94 % (No. 101)
Grade B awarded based on DRI/RDA, not clinical trials.

Recommendation 12.4: Parenteral nutrition should provide 60–100 μg selenium per day.

Grade of recommendation B – Strong consensus 91 % r (No. 102)
References [24,127,128]

12.3. When and how to provide additional amounts

Recommendation 12.5: A value of plasma selenium <0.4 μmol/l (<32 μg/l) should prompt selenium administration, starting with 100 μg/day (enteral or IV): the duration of administration will depend on response.

Grade of recommendation GPP – Strong consensus 100 % (No. 143)

Recommendation 12.6: In a patient without an inflammatory response (e.g., CRP <20 mg/l), a plasma selenium concentration of <0.75 μmol/l should trigger selenium administration (repletion).

Grade of recommendation GPP – Strong consensus 100 % (No. 144)

Comment: Patients who are depleted because of a recent reduced intake may require twice the normal daily amount (up to 200 μg/day), with monitoring of plasma selenium level. If the gastrointestinal tract is available, this can be given orally. Burn patients who have high losses of selenium, benefit from large IV supplies of around 375 μg/day, with more rapid healing and fewer infections [40]. Patients with other major trauma, and cardiac surgery may similarly benefit from a supplement of 275 μg/day [129]. Patients receiving renal replacement therapy have increased losses and oxidative stress and will require increased amounts [44].

Recommendation 12.7: Considering the good enteral absorption, and in absence of contraindication, the enteral route can be used with doses starting at 100 μg/day. In case of plasma selenium <0.4 μmol/l (30 μg/l) the IV route may be used for rapid correction: up to 400 μg/day may be required for at least 7–10 days, and status then be rechecked.

Grade of recommendation 0 – Strong consensus 100 % (No. 145)
References [125,130–132]

13. Zinc

More than 300 zinc metalloenzymes are present in biology, with essential roles in virtually all metabolic pathways [133–135]. Some examples in man include carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases and alcohol dehydrogenase. Zinc-finger proteins are central to the control of transcription of DNA into RNA. The key roles of zinc in protein and nucleic acid synthesis explain the failure of growth and impaired wound healing observed in individuals with zinc deficiency. Zinc is also part of several aspects of the antioxidant defense system.

Deficiency is caused by inadequate intake, increased requirements, malabsorption, increased losses and impaired utilization. Children, pregnant and lactating women have increased requirements and thus are at increased risk of depletion [136]. The clinical features of severe deficiency include alopecia, skin rash, growth retardation, delayed sexual development and bone maturation, impaired wound healing and immune function, diarrhea, and blunting of taste and smell [135,137].

Zinc deficiency affects both innate and adaptive immunity [138]. All immune cells are affected. T cell functions and the balance between the different T helper cell subsets are particularly susceptible to changes in zinc status. While acute zinc deficiency alters innate and adaptive immunity, chronic deficiency increases inflammation [138].

The clinical feature of zinc toxicity relates to the route and the dose of exposure and differs between acute and chronic exposure. Symptoms appear when ingestion exceeds 1 to 2 g of zinc. Toxic exposures can occur through gastrointestinal, dermal, respiratory, and parenteral routes through erroneously prepared parenteral nutrition [139].

13.1. When and what to measure

Recommendation 13.1: Zinc measurement should be done:

- In patients with increased gastrointestinal and/or skin losses
- on commencing long term PN and repeated as required depending on the presence of conditions associated with risk of deficiency.
- in patients on long-term PN, every 6–12 months

Grade of recommendation GPP – Consensus 88 % (No. 58)

Recommendation 13.2: Plasma zinc shall be used to confirm clinical zinc deficiency and to monitor adequacy of provision. Simultaneous determination of CRP and albumin is required for interpretation.

Grade of recommendation A – Strong consensus 91 % (No. 28)
Grade A awarded based on biochemistry, not clinical trials

13.2. How much to provide in typical EN and PN

Recommendation 13.3: Enteral nutrition shall provide at least 10 mg per day in 1500 kcal.

Grade of recommendation A – Strong consensus 97 % (No. 103)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 13.4: Parenteral nutrition should provide 3–5 mg zinc IV per day in patients without abnormal losses.

Grade of recommendation B – Strong consensus 88 % (No. 104)
References [24,140]

13.3. When and how to provide additional amounts

Recommendation 13.5: In patients on parenteral nutrition who have gastrointestinal losses (fistulae, stomas, and diarrhea), while nil per mouth, IV doses up to 12 mg per day can be used and are usually sufficient to maintain the status: this addition will be required for as long as gastrointestinal losses persist.

Grade of recommendation 0 – Strong consensus 100 % (No. 166)
Reference [140]

Recommendation 13.6: Patients with major burns >20 % body surface area have increased requirements due to exudative losses: 30–35 mg/day IV for 2–3 weeks should be provided.

Grade of recommendation B – Strong consensus 91 % (No. 151)
References [40,141]

Recommendation 13.7: In acquired zinc deficiency, 0.5–1 mg/kg per day of elemental zinc (Zn^{2+}), can be given orally for 3–4 months. Organic compounds such as zinc histidinate, zinc gluconate and zinc orotate show a comparatively better tolerability than inorganic zinc sulfate and zinc chloride.

Grade of recommendation: GPP – Consensus 82 % (No. 146)

Recommendation 13.8: In acrodermatitis enteropathica, a lifelong oral intake of 3 mg/kg per day of elemental zinc (Zn^{2+}) may be provided, with the dosage adjusted accordingly to plasma or serum zinc levels.

Grade of recommendation 0 – Strong consensus 94 % (No. 158)
Reference [142]

Recommendation 13.9: Oral, enteral and parenteral routes of administration can be used, route depending on gastrointestinal function. Supplementation can be combined with nutritional support or provided separately.

Grade of recommendation GPP – Strong consensus 97 % (No. 147)

14. Thiamine (vitamin B1)

Thiamine is a water-soluble vitamin essential for carbohydrate metabolism and energy metabolism [143], being a cofactor of enzymes involved in the production of ATP and the synthesis of essential cellular molecules, synthesis of various neurotransmitters and nucleic acids, and control of oxidative stress. In humans, body stores are limited, resulting in dietary intake dependency.

Thiamine deficiency is a major public health concern in several countries [143]. Clinical thiamine deficiency may present with signs and symptoms involving the neurological, and cardiovascular systems [143,144]. The neurological symptoms range from mental changes such as apathy, decrease in short-term memory, confusion, and irritability to cognitive deficits and the Wernicke-Korsakoff encephalopathy, optic neuropathy, and central pontine myelinolysis [145]. The involvement of other organs manifests as in beriberi, congestive heart failure, or unexplained metabolic lactic acidosis [146]. Among the thiamine disorders, the refeeding syndrome is of particular concern in inpatients and is associated with increased mortality [147–150].

Thiamine is among the MNs at highest risk for deficiency [151,152]. Patients at risk are numerous and include malnutrition, poor oral intake and chronic alcohol consumption, malignancies,

and increased metabolic requirements (pregnancy) [146]. Reduced gastrointestinal absorption due to disease or intestinal resections, increased gastrointestinal or renal losses [153], obesity pre- and post-bariatric surgery [154], should also be considered. Critical illness is a risk condition with its multiple metabolic challenges: deficiency or depletion may be found in over 90 % of patients [155,156].

No toxicity. The only effect of high doses is increased urinary excretion [157,158].

14.1. When and what to measure

Recommendation 14.1: RBC or whole blood thiamine should be determined in

a) patients suspected of deficiency in the context of cardiomyopathy and prolonged diuretic treatment
b) patients undergoing a nutritional assessment in the context of prolonged medical nutrition, and post-bariatric surgery
c) refeeding syndrome
d) encephalopathy

Grade of recommendation 0 – Consensus 90 % (No. 29)
References [147–149,156,159,160]

Recommendation 14.2: Thiamine status shall be determined by measuring RBC or whole blood thiamine diphosphate (ThDP).

Grade of recommendation A – Consensus 90 % (No. 4)
Grade A awarded based on biochemistry, not clinical trials.

Comment: Thiamine is found under five forms: the active form is called thiamine diphosphate (ThDP or thiamine pyrophosphate (TPP) [1]. If RBC or whole blood ThDP determination is not available, measurement of red cell transketolase and its activation by thiamine may be considered. Thiamine status determination in erythrocytes may be more reliable in the presence of inflammation [161]. In patients on diuretic therapy, low TPP levels are present in 18 % on intensive care unit (ICU) admission [162].

14.2. How much to provide in typical EN and PN

Recommendation 14.3: Enteral nutrition shall provide 1.5 to 3 mg per day of vitamin B1 in patients receiving 1500 kcal per day.

Grade of recommendation A – Strong consensus 92 % (No. 59)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 14.4: Parenteral nutrition should provide at least 2.5 mg per day.

Grade of recommendation B – Strong consensus 92 % (No. 59)
References [72,163]

Comment: in “mild deficiency” or depletion, identified by low dietary intakes and low blood ThDP, but no clinical symptoms, an intake of 10 mg per day for one week should be prescribed [164].

14.3. When and how to provide additional amounts

Recommendation 14.5: In patients admitted to emergency or intensive care, the administration of thiamine (100–300 mg/day IV) should be prescribed without hesitation from admission for 3–4 days.

Grade of recommendation B – Consensus 80 % (No. 105, No. 148)
References [163,165–167]

Recommendation 14.6: In patients admitted on the ward with any suspicion of reduced food intake during the previous days or high alcohol consumption, thiamine 100–300 mg/day should be administered by either oral or IV route.

Grade of recommendation B – Strong consensus 92 % (No. 106)
Reference [168]

Recommendation 14.7: As thiamine is well absorbed (except in alcohol related gastritis), thiamine can be administered orally, enterally, or IV. Nevertheless, considering the severity of acute deficiency symptoms, using the IV route is the most efficient, providing 3 × 100–300 mg per day.

Grade of recommendation 0 – Consensus 88 % (No. 107)
Reference [149,168]

15. Riboflavin (vitamin B2)

Riboflavin (vitamin B2) is involved in redox reactions and antioxidant functions, metabolism of other B vitamins (niacin, B6, B12, and folate), immunity (antibody production and immunomodulation) [33] and energy production. Intracellular metabolism involves phosphorylation of riboflavin to form the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which account for most of riboflavin in plasma and tissues.

Deficiency is manifested with oral-buccal lesions, seborrheic dermatitis. Other manifestations are ocular and normochromic, normocytic anemia and marrow aplasia [169]. There is evidence that poor riboflavin status interferes with iron handling and contributes to the etiology of anemia when iron intakes are low [169]. Riboflavin deficiency is frequently associated with pyridoxine, folate, and niacin deficiencies [10,169].

Patients at risk of deficiency are those with, thyroid dysfunction, diabetes, renal disease, alcoholism, and in pregnancy, lactation, and in the elderly. Also, patients with surgery, trauma, burns, or fractures, and patients on psychotropic drugs, tricyclic antidepressants, or barbiturates [10]. Patients with anorexia nervosa who avoid dairy products area can be at risk for deficiency [10]. In old adult patients, low levels, and at-risk levels of riboflavin have been described probably due to decreased intake of dairy products and alteration in absorption and metabolism.

Toxicity: Riboflavin consumed orally from the diet or from most multivitamin supplements rarely causes side effects (eventually yellow-colored urine).

15.1. When and what to measure

Recommendation 15.1: Assessment of riboflavin status can be required when there is clinical suspicion of deficiency.

Grade of recommendation GPP – Strong consensus 96 % (No. 30)

Recommendation 15.2: The riboflavin status can be assessed by the glutathione reductase activity in RBC.

Grade or recommendation 0 – Strong consensus 96 % (No. 5)
Grade 0 awarded based on biochemistry, not clinical trials

Comment: Red blood cell flavin adenine dinucleotide (FAD) is another validated method of assessment, especially in the context of inflammation. Regular monitoring of riboflavin status is not

required. Deficiency is manifested with oral-buccal lesions and seborrheic dermatitis of the face, trunk, and scrotum. Other manifestations are ocular lesions and anemia and marrow aplasia.

15.2. How much to provide in typical EN and PN

Recommendation 15.3 Enteral nutrition shall provide at least 1.2 mg per day of riboflavin in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 61)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 15.4: Parenteral nutrition should provide 3.6–5 mg riboflavin per day.

Grade of recommendation B – Strong consensus 96 % (No. 62)
Reference [170]

15.3. When and how to provide additional amounts

Recommendation 15.5: Additional amounts of riboflavin can be provided as multivitamin pills in the following cases:

- Suspected or proven clinical deficiency
- Patients at risk of deficiency
- In patients with deficiencies of other group-B vitamins
- In patients with multiple acyl-Coenzyme A dehydrogenase deficiency (MADD) as some of them are sensitive to this cofactor

Grade of recommendation GPP – Strong consensus 100 % (No. 108, No. 149)

Recommendation 15.6: Riboflavin 5–10 mg/day can be used orally in case of deficiency.

Grade of recommendation GPP – Strong consensus 96 % (No. 109)

Recommendation 15.7: In cases of clinical riboflavin deficiency, IV administration of 160 mg of riboflavin for four days may be necessary.

Grade of recommendation GPP – Strong consensus 94 % (No. 110)

Recommendation 15.8: In MADD patients, riboflavin can be given at doses of 50–200 mg/day.

Grade of recommendation GPP – Consensus 87 % (No. 111)

16. Niacin (vitamin B3)

Niacin is a collective term for nicotinic acid and nicotinamide. All tissues convert absorbed niacin into its main metabolically active form, the coenzyme NAD. More than 400 enzymes require NAD to catalyze reactions in the body. Niacin helps to convert nutrients into energy, create cholesterol and fats, create and repair DNA, and exert antioxidant effects [171,172].

Causes of niacin deficiency include inadequate oral intake, poor bioavailability from grains, defective tryptophan absorption, carcinoid tumors, metabolic disorders, and the long-term use of chemotherapeutic treatments [173]. Some secondary causes include chronic alcoholism and general malabsorptive states such as prolonged diarrhea [174].

Severe niacin and/or tryptophan deficiency leads to a variety of clinical symptoms, including diarrhea, dermatitis and dementia, collectively known as “pellagra” or “the three D disease and even death (four D) if not recognized and treated promptly [175,176].

Toxicity: The well-known side effect of niacin is flushing (face, arms, and chest), which typically occurs within 30 min of ingestion and abates after 60 min [177]. Niacin can also cause serious hepatotoxicity that may evolve into multiple organ failure. Niacin associated hepatotoxicity is generally related to ingestion of around 3 g per day. In contrast, the more common symptom of flushing can occur at doses as low as 30 mg per day [178].

16.1. When and what to measure

Recommendation 16.1: Blood or tissue NAD levels may be measured in case of clinical symptoms, including diarrhoea, dermatitis, and dementia (Pellagra disease).

Grade of recommendation GPP – Consensus 89 % (No. 31)

Recommendation 16.2: Blood or tissue NAD shall be used as a measure of niacin status.

Grade of recommendation A – Strong consensus 91 % (No. 6)
Grade A awarded based on biochemistry, not clinical trials.

Comment: Since measurement may be difficult to organize, storing a blood sample and awaiting the effects of niacin supplements on symptoms may be a pragmatic alternative.

16.2. How much to provide in typical EN and PN

Recommendation 16.3: Enteral nutrition shall provide 18 to 40 mg per day of niacin in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 63)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 16.4: Parenteral nutrition should provide at least 40 mg of niacin per day.

Grade of recommendation B – Strong consensus 95 % (No. 64)
Reference [170]

16.3. When and how to provide additional amounts

Recommendation 16.5: When there is suspicion of niacin deficiency from at risk clinical history and/or presence of signs or symptoms, higher doses may be required.

Grade of recommendation GPP – Strong consensus 95 % (No. 112)

Recommendation 16.6: The oral/enteral route should be used whenever the gastrointestinal tract is functional. In malabsorption and short bowel, the parenteral route can be used.

Grade of recommendation GPP – Strong consensus 93 % (No. 113)

Comment: recent evidence points to a relation between impaired NAD + biosynthesis and acute kidney injury (AKI) after major vascular and cardiac surgeries [179,180]. Tryptophan (precursor of NAD) or nicotinamide supplementation have been shown to diminish renal injury in ischemia-induced AKI, opening supplementation perspectives.

17. Pantothenic acid (vitamin B5)

Pantothenic acid is a constituent of the coenzyme A (CoA) and acyl carrier protein (ACP) and therefore is involved in numerous biochemical processes in oxidative respiration, lipid metabolism, synthesis of steroids, acetylated molecules (amino acids, carbohydrates) as well as prostaglandins [181].

Naturally occurring pantothenic acid deficiency is very rare and observed only in conditions of severe malnutrition. Severe deficiency can cause numbness and burning of the hands and feet, headache, extreme tiredness, irritability, restlessness, sleeping problems, stomach pain, heartburn, diarrhea, nausea, vomiting, and loss of appetite.

Toxicity of pantothenic acid is rare, and no Tolerable Upper-Level Intake (UL) has been established.

17.1. When and what to measure

Recommendation 17.1: Pantothenic acid blood determination should be performed in the context of neurological symptom investigations.

Grade of recommendation GPP – Consensus 86 % (No. 32)

Comment: Severe deficiency can cause numbness and burning of the hands and feet, headache, extreme tiredness, and multiple non-specific symptoms.

Recommendation 17.2: Pantothenic acid shall be determined in blood.

Grade of recommendation A – Strong consensus 93 % (No. 7)
Grade A awarded based on biochemistry, not clinical trials.

17.2. How much to provide in typical EN and PN

Recommendation 17.3: Enteral nutrition should deliver at least 5 mg pantothenic acid per day when providing 1500 kcal.

Grade of recommendation B – Strong consensus 95 % (No. 65)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 17.4: Parenteral nutrition should deliver at least 15 mg pantothenic acid per day.

Grade of recommendation B – Strong consensus 98 % (No. 66)
Reference [182]

17.3. When and how to provide additional amounts

Recommendation 17.5: In the context of atypical neurological symptoms additional pantothenic acid may be delivered along with other B vitamins.

Grade of recommendation GPP – Strong consensus 91 % (No. 114, No. 163)

18. Pyridoxine (vitamin B6)

The name Vitamin B6 refers to a group of six water-soluble pyridine compounds (B6 vitamers) [183]. The biologically active form is pyridoxal phosphate (PLP), which serves as coenzyme for more than 160 enzymatic reactions. These reactions include transaminations, racemizations, decarboxylations and aldol cleavage [183], affecting carbohydrate, protein, and lipid metabolism. The most important function of active, phosphorylated PLP in the cell is related to the biosynthesis as well as the degradation of amino acids, which is central to transamination reactions [184].

Deficiency can cause a variety of diseases [185], including seborrheic dermatitis with cheilosis and glossitis, microcytic anemia, epileptiform convulsions, confusion, and/or depression, and angular stomatitis.

Populations with the greatest risk for deficiency include alcoholics, renal dialysis patients [186,187], the elderly, post-operative, infections, critical illness [188], pregnancy, and people receiving medical therapies that inhibit vitamin activity (i.e., isoniazid, penicillamine, anti-cancer, corticosteroids, anticonvulsants). Deficiency has been observed during isoniazid therapy [189], HIV infection [190], severe alcoholic hepatitis [191], postoperative delirium, migraine attacks, and thymoglobulin immunosuppression [1].

Toxicity: No adverse effects due to high food intakes of pyridoxine have been reported. Clinical signs observed in case of excess pyridoxine are sensory neuropathy with ataxia or areflexia, impaired cutaneous and deep sensations, and dermatologic lesions.

18.1. When and what to measure

Recommendation 18.1: Measurement of pyridoxine should be done in presence of signs of pyridoxine deficiency (such as glossitis, sensory ataxia, seizures).

Grade of recommendation GPP – Strong consensus 95 % (No. 33)

Recommendation 18.2: Pyridoxine (B6) status shall be determined by measuring plasma pyridoxal phosphate (PLP) levels.

In seriously ill patients or in presence of inflammation, red cell PLP shall be measured.

Grade of recommendation A – Strong consensus 95 % (No. 8)
Grade A awarded based on biochemistry, not clinical trials.

18.2. How much to provide in typical EN and PN

Recommendation 18.3: Enteral nutrition shall deliver at least 1.5 mg pyridoxine per day in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 67)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 18.4: Parenteral nutrition should deliver 4 to 6 mg pyridoxine per day.

Grade of recommendation B – Strong consensus 98 % (No. 68)
Reference [170]

18.3. When and how to provide additional amounts

Recommendation 18.5: In the context of isoniazide overdose or glycol poisoning, a high dose of pyridoxine should be part of the therapy.

Grade of recommendation GPP – Strong consensus 95 % (No. 115, No. 161)

19. Biotin (vitamin B7)

Biotin can be found in all cells of the human body. It plays an important role in the metabolism of fatty acids, glucose, and amino acids as it is a cofactor for five carboxylases that are critical for their metabolism [192]. Biotin sufficiency is essential for normal fetal development.

Biotin deficiency is rare in the general population due to its wide availability. Biotin deficiency leads to dermal (i.e. dermatitis, alopecia) as well as neurological complications such as ataxia [193,194]. Conditions at risk of developing deficiency include chronic alcohol consumption, malabsorption in the context of Crohn's disease and colitis, short bowel syndrome, celiac disease, severe malnutrition, smoking, and pregnancy. Long-term antibiotic use may destroy bacteria that produce biotin.

Toxicity of biotin is unlikely, and no UL has been established.

19.1. When and what to measure

Recommendation 19.1: Biotin status may be assessed in presence of clinical symptoms suggesting biotin deficiency (i.e. dermatitis, alopecia, or neurological symptoms) and a history suggestive of inadequate intake.

Grade of recommendation GPP – Strong consensus 95 % (No. 34)

Comment: Conditions at risk of developing deficiency include chronic alcohol consumption, malabsorption in the context of Crohn's disease and colitis, short bowel syndrome, celiac disease, severe malnutrition, smoking, and pregnancy. Long-term antibiotic use may destroy bacteria that produce biotin.

Recommendation 19.2: Biotin status shall be determined by the direct measure of blood and urine biotin and should be completed by the determination of biotinidinase activity.

Grade of recommendation A – Strong consensus 95 % (No. 9)
Grade A awarded based on biochemistry, not clinical trials.

19.2. How much to provide in typical EN and PN

Recommendation 19.3: In enteral nutrition at least 30 μg of biotin per day should be provided in 1500 kcal.

Grade of recommendation B – Strong consensus 100 % (No. 69)
Grade A awarded based on biochemistry, not clinical trials

Recommendation 19.4: In parenteral nutrition, vitamin additives should provide 60 μg biotin per day.

Grade of recommendation B – Strong consensus 98 % (No. 70)
Reference [195]

19.3. When and how to provide additional amounts

Recommendation 19.5: Breast-feeding mothers should receive an intake of at least 35 μg biotin per day orally.

Additional amounts may also be needed in patients on renal replacement therapy.

Grade of recommendation GPP/0 – Strong consensus 100 % (No. 116, No. 167)
Reference [194]

Recommendation 19.6: Additional amounts of biotin can be administered either orally, enterally or IV depending on the intestinal function.

Grade of recommendation GPP – Strong consensus 95 % (No. 117)

20. Folate and folic acid (vitamin B9)

Folate is a generic term referring to a family of molecules [196], which include both the naturally occurring MN folates and synthetic forms (folic acid). Biologically active folate forms include folinic acid and 5-methyltetrahydrofolate (5-MTHF) [196].

Most symptoms of folate deficiency overlap with cobalamin deficiency, i.e. megaloblastic anemia, and pancytopenia, glossitis, angular stomatitis, oral ulcers, neuropsychiatric manifestations, including depression, irritability, insomnia, cognitive impairment, psychosis, anorexia, and fatigue [197]. Deficiency in one or both vitamins cause megaloblastic anemia [198].

Cases of isolated clinical folate deficiency are extremely rare. In patients with chronic kidney disease and/or on hemodialysis, folic acid and vitamin B12 metabolism are impaired, and it has long been known that their requirements are significantly higher than standard DRI [199]. Some patients, especially diabetics, may require as much as 15 mg per day [22]. Hyper-homocysteinemia is common, and folic acid together with vitamin B12 is critical for the conversion of homocysteine to methionine [200]. Folic acid has also been shown to improve endothelial function in chronic kidney disease [201].

Toxicity: Oral administration of folic acid in recommended dosage is considered non-toxic. Due to the proliferative effects, folic acid might increase cancer risk and progression. Moreover, it is said to cause insulin resistance in children, interact with epilepsy medication, mask a vitamin B12 deficiency, and be hepatotoxic [202]. Excess folic acid is excreted in the urine.

20.1. When and what to measure

Recommendation 20.1: In patients with macrocytic anemia or at risk of malnutrition, folic acid status should be measured at least once at first assessment and repeated within 3 months after supplementation to verify normalization.

Grade of recommendation GPP – Strong consensus 97 % (No. 35)

Recommendation 20.2: In diseases known to increase the needs for folate, folate status should be measured every 3 months until stabilization, and then once a year.

Grade of recommendation GPP – Strong consensus 96 % (No. 36)

Recommendation 20.3: Folate status shall be assessed in plasma or serum (short-term status), or RBC (long-term status) using a method validated against the microbiological assay.

Grade of recommendation A – Strong consensus 96 % (No. 10)
Grade A awarded based on biochemistry, not clinical trials.

Comment: The gold standard method of measuring folate is microbiological assay with *Lactobacillus rhamnosus.* Analysis of homocysteine at the same time improves the interpretation of laboratory measurements.

20.2. How much to provide in typical EN and PN

Recommendation 20.4: Enteral nutrition shall provide 330–400 μg Dietary Folate Equivalents (DFE) per day in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 71)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 20.5: Parenteral nutrition should provide 400–600 μg per day folic acid.

Grade of recommendation B – Strong consensus 100 % (No. 72)
Grade B awarded based on DRI/RDA, not clinical trials

20.3. When and how to provide additional amounts

Recommendation 20.6: In case of dietary deficiency or chronic hemodialysis, 1–5 mg folic acid per day may be given orally.

Grade of recommendation 0 – Strong consensus 100 % (No. 118)
Reference [199]

Comment: In case of deficiency, the oral administration should last four months, or until the reason for the deficiency is corrected. In patients on chronic hemodialysis with hyperhomocysteinemia, increased amounts may be required for prolonged periods.

Recommendation 20.7: For the prevention of neural tube defects, women who desire to have children or women not taking oral contraceptives and living in countries without folic acid fortification of staple foods shall take folic acid supplements (400 μg/day) periconceptionally/whilst of childbearing age.

Grade of recommendation A – Strong consensus 98 % (No. 119, No. 168)
References [203,204]

Recommendation 20.8: Additional amounts of folic acid should be administered orally. In case of ineffective oral treatment or intolerance, folic acid can be given (0.1 mg/day), subcutaneously, IV, or intramuscular (IM).

Grade of recommendation GPP – Strong consensus 95 % (No. 120)

21. Cobalamin (vitamin B12)

Vitamin B12 (cobalamin) is an essential water-soluble MN synthesized by fungi and microorganisms, and in the stomach of ruminant animals. Humans are totally dependent upon animal sources or fortification [205,206]. Cobalamin absorption is complex, and depends on the gastric intrinsic factor and receptor-mediated endocytosis [207].

Cobalamin is a cofactor for two enzymes in humans: methionine synthase and methyl malonyl-CoA mutase [205]. These pathways are essential for mitochondrial metabolism, immune response, DNA integrity, neuronal myelin sheath integrity, and synthesis of neurotransmitters.

The prevalence of cobalamin deficiency is estimated to be around 10–26 % in the general population in Western countries, with old adults being at highest risk [208]. Deficiency is largely underdiagnosed and might reach 75 %–90 % of vegetarian or vegan diet communities [209,210].

Inadequate intake is the main cause of low status worldwide [208]. Absorption of cobalamin from food requires normal stomach, pancreas, and small intestine function [211]. The most prevalent causes of deficiency are an autoimmune condition known as pernicious anaemia, resulting from a lack of intrinsic factor and, and food-bound cobalamin malabsorption. Both conditions are also common with chronic atrophic gastritis, which affects around 10–30 % of people over 60 years [209]. Long-term diabetic metformin treatment exposes to risk of deficiency [212,213]. Post-bariatric surgery patients are at high risk: symptoms manifest after a few months without adequate complementation: the requirements are far superior to DRI.

The manifestations of deficiency are primarily haematological or neuropsychiatric [209], with a variety of non-specific symptoms.

Toxicity: There is no upper toxicity limit for cobalamin and no reports of acute toxicity in oral or parenteral cobalamin supplementation or treatment.

21.1. When and how to measure or monitor

Recommendation 21.1: Cobalamin deficiency should be excluded in all patients who present with anaemia, or isolated macrocytosis, established diagnosis of polyneuropathies, neurodegenerative diseases or psychosis.

Grade of recommendation GPP – Strong consensus 98 % (No. 37)

Recommendation 21.2: In all patients at risk, or on treatment with cobalamin, replenishment adequacy should be assessed at least annually by resolution of clinical symptoms and available laboratory markers.

Grade of recommendation GPP – Strong consensus 98 % (No. 38)

Recommendation 21.3: Adult patients at risk or suspected of cobalamin deficiency should be screened with the combination of at least two biomarkers (holo-TC, methyl malonic acid (MMA)), with serum cobalamin as an alternative.

Grade of recommendation B – Strong consensus 92 % (No. 11)
Grade B awarded based on DRI/RDA, not clinical trials.

Recommendation 21.4: Patients with autoimmune diseases or with glossitis, anaemia and neuropathy should be screened for pernicious anaemia with the presence of anti-intrinsic factor antibodies regardless of cobalamin levels.

Grade of recommendation GPP – Strong consensus 100 % (No. 12)

21.2. How much to provide in typical EN and PN

Recommendation 21.5: Enteral nutrition shall provide at least 2.5 μg cyanocobalamin per day in 1500 kcal.

Grade of recommendation A– Strong consensus 97 % (No. 73)

Recommendation 21.6: Parenteral nutrition should provide at least 5 μg cyanocobalamin per day.

Grade of recommendation GPP– Strong consensus 97 % (No. 74)

21.3. When and how to provide additional amounts

Recommendation 21.7: Breast-feeding mothers shall receive an intake of at least 2.8 μg cyanocobalamin per day orally.

Grade of recommendation A – Strong consensus 100 % (No. 121)

Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 21.8: Patients with compromised cobalamin absorption should receive life-long supplements either as a daily dose of 350 μg cobalamin, or IM injections of 1000–2000 μg of cobalamin every 1 to 3 months.

Grade of recommendation GPP – Strong consensus 100 % (No. 122, No. 164)

Recommendation 21.9: In presence of acute clinical symptoms of deficiency, anti-intrinsic factor antibodies, a history of total gastrectomy or continuous malabsorptive diseases, the IM route should be used. Starting with high doses of 1000 μg cobalamin every second day for 2 weeks (or daily for 5 days).

Grade of recommendation GPP – Strong consensus 100 % (No. 123)

Comment: Intranasal and sublingual administration are alternative routes [54]. The conditions include, but are not limited to, short bowel syndrome, bariatric surgery, Crohn's diseases, gastrectomy, atrophic gastritis, and ileal resection. Treatment should be continued at least twice monthly until resolution of all clinical signs and/or etiopathogenetic factors (including resolution of macrocytosis). Monitoring blood potassium should be part of repletion therapy.

22. Vitamin A (retinol)

This liposoluble vitamin is a prohormone. The precursor Retinol is transformed into the active Retinoic acid and retinal. Retinol and retinal are responsible for vision and reproductive function. Retinoic acid controls cellular growth and differentiation [214]. The active metabolites, activate gene expression in more than 500 target genes [214]. Vitamin A plays an important role in the immune system [215]. Retinol binding protein (RBP) is a negative acute phase protein, which leads to a fall in serum retinol [216].

Vitamin A deficiency is a public health problem in most developing countries due to malnutrition, especially in children and pregnant women [217]. Before the well-known ophthalmic signs of deficiency (including night blindness, xerophthalmia), there is an increased susceptibility to infections, especially of the respiratory tract as the main symptom [218,219]. The intestinal immune and barrier function are also impaired [220].

Deficiency should be sought in liver diseases, chronic alcohol consumption, chronic kidney diseases, short bowel syndrome, and obesity.

Toxicity: Acute toxicity develops when quantities of natural vitamin A above 300,000 IU (adults) or > 60,000 IU (children) are ingested within a few hours or days [221]. Symptoms include increased intracranial pressure, nausea, headaches, pain in joints and bones. Chronic toxicity results from the ingestion of daily amounts of >25,000 IU for more than 6 years or >100,000 IU for more than 6 months, with a high inter-individual variability [222]. Above 14,000 μg/d for longer time periods may cause hepatotoxic effects.

22.1. When and what to measure

Recommendation 22.1: Serum retinol and retinyl esters (if available) measurements should be considered in patients being investigated for malabsorption.

Grade of recommendation B – Strong consensus 96 % (No. 41, No. 165)
Grade A awarded based on physiology, not clinical trials

Comment: Malabsorption/reduced binding protein/reduced storage may occur in the context of several diseases including persistent critical illness

Recommendation 22.2: Vitamin A status shall be determined by measuring serum retinol.

Grade of recommendation A – Strong consensus 95 % (No. 14)
Grade A awarded based on biochemistry, not clinical trials.

Comment: interpretation can be improved by also measuring CRP and retinol binding protein

22.2. How much to provide in typical EN and PN

Recommendation 22.3: Enteral nutrition shall provide 900–1500 μg retinyl esters (RE) per day, when providing 1500 kcal per day.

Grade of recommendation A - Strong consensus 97 % (No. 77)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 22.4: Parenteral nutrition should provide 800 to 1100 μg RE per day.

Grade of recommendation B– Strong consensus 97 % (No. 78)
Reference [85]

22.3. When and how to provide additional amounts

Recommendation 22.5: In conditions causing fat malabsorption, prevention of deficiency with oral supplements may be considered.

Grade of recommendation GPP – Strong consensus 97 % (No. 126)

23. Vitamin C (ascorbic acid)

Vitamin C has numerous functions, which are all based on electron donation [223–225]. It is the most potent water-soluble antioxidant, which directly scavenges radicals, mitigates the production of oxygen radicals, and recycles other antioxidants. Furthermore, vitamin C is an important cofactor/cosubstrate for the biosynthesis of neurotransmitters, cortisol, peptide hormones, and collagen. It promotes endothelial collagen synthesis, and maintains endothelial vasodilation and barrier function [226]. It limits the inflammatory response and ischemia-reperfusion injury, and improves immunity [227] and wound healing [1].

Clinical conditions with increased inflammation and oxidative stress, such as sepsis, trauma, cardiac arrest, major surgery, and burns are associated with a high risk of depletion. Very low plasma levels are observed in a substantial proportion of patients within hours of acute disease/injury [1,228–232]. In critically ill patients, low plasma concentrations are associated with severity of oxidative stress [233], organ failure, and mortality [230].

Chronic depletion is encountered in patients after bariatric surgery [234], alcohol abuse [235], chronic dialysis, smoking [236], chronic inflammation and oxidative stress, smoking, heart failure [237], severe chronic obstructive pulmonary disease (COPD), chronic dialysis, and malabsorption [1].

Symptoms of classical scurvy (such as anemia, poor wound healing, myalgia and bone pain, spongy and purplish gums that are prone to bleeding, loose teeth) are rarely seen in hospital settings, where deficiency easily goes unnoticed.

Toxicity: Supplements are contraindicated in blood disorders like thalassemia, G6PD deficiency, sickle cell disease, and hemochromatosis [238]. Adverse events include urinary calcium oxalate crystallization, renal stone formation and nephropathy due to increased oxalate excretion in susceptible patients receiving higher than repletion doses for longer periods of time.

23.1. When and what to measure

Recommendation 23.1: Plasma vitamin C concentrations may be measured in all patients with clinical suspicion of scurvy or chronic low intake.

Grade of recommendation GPP – Consensus 87 % (No. 39)

Recommendation 23.2: Measurement of plasma vitamin C is not recommended in critical illness or severe inflammation, due to the difficulty in interpretation of results.

Grade of recommendation GPP – Strong consensus 92 % (No. 40)

Recommendation 23.3: Vitamin C status should be assessed by a measure of L-ascorbic acid (AA) or total plasma vitamin C (sum of AA and dehydroascorbic acid (DHAA).

Grade of recommendation B – Strong consensus 100 % (No. 13)
Grade B awarded based on biochemistry, not clinical trials

Comment: The determination of plasma ascorbic acid necessitates considerable logistical and analytical efforts [239]. The high susceptibility of vitamin C to degradation related to temperature, light, pH, dissolved oxygen, and the presence of oxidizing/reducing agents, requires specific pre-analytical precautions. But deficiency is widespread [1]. A clinical trial of vitamin C of about 1g/day for at least one week, should not be delayed in the presence of clinical symptoms.

23.2. How much to provide in typical EN and PN

Recommendation 23.4: Enteral nutrition shall provide at least 100 mg of vitamin C per day in 1500 kcal.

Grade of recommendation A– Strong consensus 97 % (No. 75)

Reference [240], additionally, grade A is awarded based on DRI/RDA, not clinical trials

Recommendation 23.5: Parenteral nutrition should provide 100 to 200 mg vitamin C per day.

Grade of recommendation GPP – Strong consensus 97 % (No. 76)

23.3. When and how to provide additional amounts

Recommendation 23.6: In patients with chronic oxidative stress (diabetes mellitus, smoking, heart failure, alcoholism, severe chronic obstructive pulmonary disease, and chronic dialysis) or malabsorption, a dose of 200–500 mg/day may be provided.

Grade of recommendation GPP - Strong consensus 92 % (No. 124)

Recommendation 23.7: During critical illness, a higher vitamin C repletion dose of 2–3 g per day may be given IV during the acute phase of inflammation.

Grade of recommendation 0 – Consensus 84 % (No. 125)
References [129,241–247]

Comment: The above 2–3 g/day dose is a metabolic concept distinct from the pharmacological doses used in sepsis trials. The recent large LOVIT-randomized controlled trial (RCT) in ICU septic patients receiving vasopressor therapy [248], showed that the high dose patients had a higher risk of death or persistent organ dysfunction at 28 days compared to placebo (44.5 vs 38.5 %; $p = 0.01$). Intriguing data pointing to the importance of the chemical form of vitamin C show that while sodium ascorbate (a base) seems effective in reducing shock symptoms and signs in ovine gram-negative sepsis model, ascorbic acid might not be due to its intense promotion of acidosis [249,250]. The chemical formulation of the vitamin C administered in the different ascorbic acid RCTs is under investigations and may provide helpful explanations for some of the outcomes [251].

24. Vitamin D (25-hydroxyvitamin D)

Vitamin D is not a classic vitamin but a steroid hormone precursor. Cutaneous endogenous production is possible from cholesterol with UV-B exposure, explaining the strong seasonal variation in vitamin D levels. Supply depends on food intake, but usually does not cover the needs. The vitamin D receptor is expressed in many body tissues including muscle (skeletal and cardiac), bone, immune system, skin, and endocrine organs, which is a major difference compared to other vitamins.

The only disease caused by vitamin D deficiency is rickets (osteomalacia in adults), which was first described in the 17th century. The definition and relevance of vitamin D deficiency, particularly in acute illness, remains debated, as the definition of deficiency is based on blood levels from studies on osteoporosis, a condition with no (or very limited) inflammation.

A level below 50–75 nmol/l (or 20–30 ng/ml) of serum/plasma 25(OH)D concentration is considered to define deficiency by the endocrine societies [1,252,253]. A cut-off <25 or <30 nmol/l (or 10/12 ng/ml) increases the risk for osteomalacia, and nutritional rickets dramatically and therefore is considered to determine severe vitamin D deficiency [253]. The risk of deficiency is elevated in patients with severe kidney or liver dysfunction, bed ridden and chronically ill patients [254]. Importantly, benefit from vitamin D supplementation can only be expected in deficiency, not in the general population [255].

Toxicity: Intoxication is rare, but has been described with 1) true overdoses, deliberate or accidental (typically single doses of millions IU or daily doses of >10,000 or even 100,000 IU), 2) manufacturing errors and 3) increased vitamin D sensitivity (i.e. CYP24A1 loss of function mutations, or idiopathic infantile hypercalcemia) [256]. Vitamin D toxicity symptoms are mediated by high calcium levels (hypercalcemia, hypercalciuria, dizziness, renal failure) [257].

24.1. When and what to measure

Recommendation 24.1: Vitamin D status may be determined in all patients considered at risk of vitamin D depletion or deficiency.

Grade of recommendation 0 – Strong consensus 92 % (No. 42)
Reference [254]

Recommendation 24.2: Status shall be determined by serum 25-hydroxyvitamin D (25(OH)D).

Grade of recommendation A – Strong consensus 95 % (No. 15)
Grade A awarded based on biochemistry, not clinical trials.

24.2. How much to provide in typical EN and PN

Recommendation 24.3: Enteral nutrition shall provide at least 1000 IU (25 μg) per day of vitamin D in 1500 kcal.

Grade of recommendation A – Strong consensus 95 % (No. 79)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 24.4: Parenteral nutrition should provide at least 200 IU (5 μg) of vitamin D per day.

Grade of recommendation B – Strong consensus 95 % (No. 80)
References [258,259]

Comment: Patients on EN frequently receive 400–800 IU/day. Although this may be adequate in some patients, the above dose is higher because patients receiving EN are likely to have higher requirements as a result of poor status due to prior illness. Some patients will have higher requirements, which should be checked by a blood determination.

24.3. When and how to provide additional amounts

Recommendation 24.5: Vitamin D in doses 4000–5000 IU (100–125 μg) per day should be administered for 2 months in patients with recurrent deficiency to achieve blood levels of 25(OH)D between 40 and 60 ng/ml. Substantially higher doses might be required.

Grade of recommendation B - Strong consensus 100 % (No. 127)
References [260,261]

Comment: Studies have suggested that these higher doses are required in patients who have recurrent deficiency with extremely low 25(OH)D levels [262]. Populations at risk include inflammatory bowel disease, obese adults, bariatric surgery, chronic liver disease, pancreatic insufficiency, chronic intestinal failure, pregnant women, and older adults. Patients with advanced and chronic kidney disease are a group requiring specialized care. Single ultra-high bolus doses are unphysiological: they upregulate catabolic processes and have been shown to be inefficient or even harmful and are therefore not recommended: Such doses may be needed upfront when time is critical (i.e. before initiation of potent osteoporosis treatment): such high bolus doses should be followed by maintenance doses (daily, weekly) to prevent vitamin D inactivation [263].

25. Vitamin E (α-tocopherol)

Vitamin E is a fat-soluble antioxidant. Alpha-tocopherol, the natural vitamin E with the highest biological activity, is a component of all biological membranes and is the most important lipid-soluble antioxidant. Its most important function is to protect membrane lipids, lipoproteins and depot fats from lipid peroxidation [264]. The activity of vitamin E is limited to the naturally occurring form, α-tocopherol, and the synthetic forms. As they are not converted to α-tocopherol by humans, the other naturally occurring forms of vitamin E (β, γ and δ-tocopherol and tocotrienols) do not contribute toward meeting requirements [122,264].

Deficiency is rare and may appear in context of severe malnutrition. Patients with fat malabsorption are at risk of inadequate supply of fat-soluble MNs [265]. Genetic causes are rare but should be sought in case of resistant deficiency [266].

In adults with fat malabsorption, early vitamin E inadequacy is generally asymptomatic [267]. Neurological symptoms are associated with balance and coordination disorders, peripheral neuropathy, and muscle weakness. Instructions to reduce fat intake as part of weight management results in a 50 % reduction in vitamin E intake [268,269].

Toxicity: There are no reports regarding parenteral vitamin E toxicity. Toxic effects from high doses of vitamin E are rare even after a high intake for several years [270]. From numerous studies on the prophylactic and therapeutic use of vitamin E, even in large supplemental oral doses (3200 IU) per day, have shown no consistent adverse effects.

25.1. When and what to measure

Recommendation 25.1: Vitamin E should be determined when there is clinical suspicion of Vitamin E deficiency. These would include cystic fibrosis, a-beta lipoproteinaemia, and thrombotic thrombocytopenic purpura. In the absence of clinical signs of deficiency, there is no indication to measure vitamin E status during PN.

Grade of recommendation B – Consensus 89 % (No. 43, No. 169)
References [265–268]

Comment: In adults with fat malabsorption, early vitamin E inadequacy is generally asymptomatic [267]. Neurological symptoms are associated with balance and coordination disorders, peripheral neuropathy, and muscle weakness.

Recommendation 25.2: To detect vitamin E deficiency, plasma α-tocopherol should be measured.

Grade of recommendation B – Strong consensus 95 % (No. 16)
Grade B awarded based on biochemistry, not clinical trials

25.2. How much to provide in typical EN and PN

Recommendation 25.3: Enteral nutrition shall provide at least 15 mg α-tocopherol per day with 1500 kcal.

Grade of recommendation A – Strong consensus 100 % (No. 81)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 25.4: Parenteral nutrition should provide at least 9 mg α-tocopherol per day.

Grade of recommendation B – Strong consensus 97 % (No, 82)
Reference [271]

25.3. When and how to provide additional amounts

Recommendation 25.5: Vitamin E should be supplemented if plasma α-tocopherol levels are below <12 μmol/l, starting with 100 mg per day depending on the cause of depletion/deficiency.

Grade of recommendation GPP – Strong consensus 92 % (No. 128)

26. Vitamin K (phylloquinone)

Vitamin K includes a group of lipid-soluble molecules that possess carboxylase enzyme cofactor activity necessary for the activation of vitamin K dependent-proteins [272]. These include the coagulation factor proteins C, S, M, Z, factors VII, IX, X and prothrombin. Vitamin K includes vitamers known as vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). While phylloquinone is produced by plants, menaquinones are synthetized by human intestinal microbiota. Vitamin K3 (menadione) is a synthetic provitamin K that requires conversion to menaquinone-4 (MK-4) to be active [273].

The most common causes of vitamin K deficiency are conditions with fat malabsorption (celiac disease, cystic fibrosis, short bowel, etc.), malnutrition, antibiotic and anticoagulant (warfarin) treatments.

Vitamin K deficiency may contribute to significant bleeding, poor bone development, osteoporosis, and increased cardiovascular disease. In normal healthy adults, 8–31 % have vitamin K deficiency. Classically, deficiency results in the prolongation of prothrombin time with impaired clotting or bleeding [1].

Toxicity: Vitamin K1 and vitamin K2 are not associated with toxicity. Rare anaphylactoid reactions with bronchospasm and cardiac arrest after IV vitamin K1 (phytonadione) administration

26.1. When and what to measure

Recommendation 26.1: The vitamin K status may be measured in at risk patients, including pathologies causing steatorrhea, prolonged use of broad-spectrum antibiotics, and chronic kidney disease.

Grade of recommendation GPP – Consensus 89 % (No. 43, No. 170)

Recommendation 26.2: Vitamin K status shall be determined by a combination of biomarkers in combination with dietary intake, as there is no agreed standard.

Grade of recommendation A – Strong consensus 95 % (No. 17)
Grade A awarded based on biochemistry, not clinical trials.

Comment: The quantification of circulating phylloquinone (vitamin K1) in blood plasma or serum remains the most used marker of vitamin K status, although being mainly a biomarker of short term phylloquinone intake.

26.2. How much to provide in typical enteral and parenteral nutrition regimen

Recommendation 26.3: Enteral nutrition in adults should provide at least 120 μg vitamin K per day with 1500 kcal.

Grade of recommendation B – Strong consensus 97 % (No. 83)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 26.4: Parenteral nutrition may provide 150 μg of vitamin K1 per day.

Grade of recommendation 0 – Strong consensus 95 % (No. 84)
References [274–276]

27. A. Non-DRI qualified: L-carnitine, choline, and CoQ10

These three micronutrients do not qualify as essential vitamins, despite insufficient or deficiency status having been shown under special clinical situations. There are no DRI for these nutrients, and they will not appear in the flowcharts.

28. B. L-carnitine

28.1. When and what to measure

Recommendation 27.1: Carnitine determination is not a routine requirement. In critically ill patients, carnitine status should be explored in presence of an unexpected loss of lean body mass, with the concomitant presence of hypertriglyceridemia and hyperlactatemia, particularly in case of prolonged parenteral nutrition or continuous renal replacement therapy.

Grade of recommendation GPP – Strong consensus 91 %

Recommendation 27.2: The simultaneous concentrations of total carnitine, free carnitine, carnitine esters and the carnitine precursors should be measured, to enable the calculation of the acyl-to-free carnitine ratio. This should only be used to confirm a clinical diagnosis and should not delay commencing supplements.

Grade of recommendation GPP – Strong consensus 91 %

28.2. How much to provide in typical enteral or parenteral nutrition regimens

Recommendation 27.3: Carnitine is not an essential nutrient: currently there is insufficient evidence to support its routine addition in enteral nutrition or parenteral nutrition.

Grade of recommendation 0 – Strong consensus 100 %
Reference [277]

28.3. When and how to provide additional amounts

Recommendation 27.4: In proven deficiency situations, the administration of L-carnitine supplementation of 2 to 5 mg/kg/day has been suggested via the route used for administration of macronutrients, until carnitine and acyl-to-free ratio revert to normal values.

Grade of recommendation GPP – Strong consensus 91 %

Comment**:** Availability of suitable supplements may be limited.
Recommendation 27.5: In case of antiretroviral drug toxicity, pharmacologic doses (50–100 mg/kg/day) may be administered.

Grade of recommendation 0 – Strong consensus 100 %
References [278,279]

29. C. Choline

29.1. When and what to measure

Recommendation 28.1: Plasma free choline may be determined in patients on home parenteral nutrition who develop unexplained liver steatosis/steatohepatitis or subclinical muscle damage with high creatine kinase levels.

Grade of recommendation GPP – Strong consensus 100 %

Recommendation 28.2: Plasma free choline can be integrated in long-term follow-up of cystic fibrosis patients.

Grade of recommendation GPP – Strong consensus 91 %

Recommendation 28.3: There is no routinely accessible biomarker in blood, although choline and its metabolites can be measured.

Grade of recommendation GPP – Strong consensus 100 %

29.2. How much to provide in typical enteral or parenteral nutrition regimens

Recommendation 28.4: Choline is not an essential nutrient. Although there is limited evidence, a dose of 400–550 mg per day has been suggested to support lipid metabolism.

Grade of recommendation 0 – Strong consensus 100 %
Reference [171]

29.3. When and how to provide additional amounts

Recommendation 28.5: In patients on home parenteral nutrition and patients presenting with unexplained liver steatosis or steatohepatitis with suspected or proven deficiency, the administration of 550 mg to 2 g/day may be considered.

Grade of recommendation 0 – Strong consensus 100 %
Reference [280]

Recommendation 28.6: In the treatment of patients with probable choline deficiency, and tolerating enteral nutrition, choline rich feeds or enteral choline preparations can be safely provided in equivalents of 500 mg–1500 mg per day for adults.

Grade of recommendation GPP – Consensus 90 %

30. D. Coenzyme Q10

30.1. When and what to measure

Recommendation 29.1: There is no clinical indication to measure plasma coenzyme Q10 (CoQ10) levels. Measurements are largely for research studies.

Grade of recommendation GPP - Strong consensus 100 %

Comment: CoQ10 is a vitamin-like compound, which is predominantly synthesized *de novo* in the human body at an estimated rate of 500 mg/day.

Recommendation 29.2: For the assessment of CoQ10 status for research purposes, the plasma CoQ10 concentration may be measured.

Grade of recommendation GPP – Strong consensus 100 %

31. Conclusion

Some MN deficiencies or inadequacies may lead to, or worsen diseases, whereas other status alterations may be the consequence of disease or their treatment. Clinicians should be aware of these combinations, and suitable consideration given to the assessment, provision, and monitoring of a group of MNs. The practical version of the 2022 guideline, focuses again separately on all essential MNs, emphasizing their individual specificities and potential importance in acute and chronic disease. This should not result in the wrong perception that MNs can be addressed separately. Micronutrients work as a web, each being responsible, often in combination, for various steps of metabolic, antioxidant, endocrine and immune responses. This is particularly well shown for immunity: Gombart et al. [281] managed to detail how the different vitamins and trace elements interact at different levels to ensure barrier, innate, and acquired immunity. The same is true for virtually all functions. Addressing the MNs globally is essential clinically and in research – the investigation of isolated MNs, ignoring the interactions will not provide real life answers.

The clinical MN data remain limited, but with progression of knowledge, their importance becomes more and more obvious. The MN products that are available on the market only allow a “one size fits all” prescription with fixed multi-micronutrient combinations. Providing the complete range of MNs is vital [282,283], but addressing specific depletion or deficiency with isolated products, is equally essential but not yet possible in most countries. The development of isolated single MN products is required which is particularly true for trace elements.

At a time where the WHO and related agencies insist on the concept that “Food is Medicine”, clinical nutrition is on the top of the pyramid of required actions [284]. This guideline should encourage research on MNs in medical nutrition therapy to make it become true.

Conflict of interest

All the authors declares no conflicts of interest.

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