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ESPEN Guideline

ESPEN guideline on nutritional support for polymorbid medical inpatients

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SUMMARY

Background: Disease-related malnutrition in polymorbid medical inpatients is a highly prevalent syndrome associated with significantly increased morbidity, disability, short- and long-term mortality, impaired recovery from illness, and cost of care.
Aim: As there are uncertainties in applying disease-specific guidelines to patients with multiple conditions, our aim was to provide evidence-based recommendations on nutritional support for the polymorbid patient population hospitalized in medical wards.
Methods: This update adheres to the standard operating procedures for ESPEN guidelines. We did a systematic literature search for 15 clinical questions in three different databases (Medline, Embase and the Cochrane Library), as well as in secondary sources (e.g. published guidelines), until July 12th. Retrieved abstracts were screened to identify relevant studies that were used to develop recommendations (incl. SIGN grading), which was followed by submission to Delphi voting.
Results: From a total of 3527 retrieved abstracts, 60 new relevant studies were analyzed and used to generate a guideline draft that proposed 32 recommendations (7x A, 11x B, 10x O and 4x GPP), which encompass different aspects of nutritional support including indication, route of feeding, energy and protein requirements, micronutrient requirements, disease-specific nutrients, timing, monitoring and procedure of intervention. The results of the first online voting showed a strong consensus (agreement of >90%) on 100% of the recommendations. Therefore, no final consensus conference was needed.
Conclusions: Recent high-quality trials have provided increasing evidence that nutritional support can reduce morbidity and other complications associated with malnutrition in polymorbid patients. The timely screening of patients for risk of malnutrition at hospital admission followed by individualized nutritional support interventions for at-risk patients should be part of routine clinical care and

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multimodal treatment in hospitals worldwide. Use of this updated guideline offers an evidence-based nutritional approach to the polymorbid medical inpatients and may improve their outcomes.

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Abbreviations

BI	Barthel Index
βHMB	β-hydroxy β-methylbutyrate
CG	Control Group
DRM	Disease-Related Malnutrition
EN	Enteral Nutrition
GLIM	Global Leadership Initiative on Malnutrition
HGS	Handgrip strength
IC	Indirect Calorimetry
IG	Intervention Group
LOS	Length Of hospital Stay
MNA(-SF)	Mini Nutritional Assessment (short form)
MUST	Malnutrition Universal Screening Tool
NRS 2002	Nutritional Risk Screening 2002
NST	Nutrition Support Team
ONS	Oral Nutritional Supplement(s)
PICO	Population of interest, Interventions, Comparisons, Outcomes
PN	Parenteral Nutrition
QoL	Quality Of Life
REE	Resting Energy Expenditure
RCT	Randomized Controlled Trial
SF-12	12-Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
SGA	Subjective Global Assessment
SIGN	Scottish Intercollegiate Guidelines Network
SNAQ	Short Nutritional Assessment Questionnaire
TEE	Total Energy Expenditure
WG	Working Group

1. Introduction

The present guideline represents an update of the original guideline on polymorbid patients from 2018 [1] and follows the Standard Operating Procedures (SOP) from European Society for Clinical Nutrition and Metabolism (ESPEN) [2]. Compared to the original guideline, the Working Group (WG) decided to keep the same twelve PICO questions for which the recommendations and associated evidence were updated and reviewed, to formulate evidence-based recommendations also for the three non-PICO questions, and to add a new question regarding biomarkers to predict treatment response to address heterogeneity as certain patients do not show the same benefit from nutritional support.

1.1. What is the definition of polymorbidity?

Although there is no universally accepted definition of polymorbidity (also known as multimorbidity), some authors define it as being the co-occurrence of at least two chronic health conditions in the same person. That is also the definition used for the purposes of this guideline, based on literature recommendations [3–5] and discussions within the guideline WG.

The health and nutrition implications of suffering from more than one disease at the same time differ from the corresponding interactions between disease and aging. Polymorbidity is often, but not necessarily, observed in older persons, in contrast to the geriatric context when multimorbidity is always combined with functional limitations and other age-related degenerative expressions. As life expectancy increases and individuals acquire a variety of chronic illnesses, polymorbidity becomes one of the main challenges that many healthcare and social services face worldwide. Additionally polymorbidity is associated with increased health service utilization and poorer health outcomes [6,7], demonstrating the relevance of proper treatment for polymorbid patients.

1.2. Why do we need to develop nutritional support guidelines for polymorbid medical inpatients?

As stated by Lefevre et al., "we know, for example, how to educate a diabetic patient, a chronic bronchitis patient, and a hypertensive patient, but we do not know, in practical terms, how to educate a patient with all three diseases" [3]. In fact, we did not know if the screening, assessment and treatment of disease-related malnutrition (DRM) in polymorbid medical inpatients should differ from the approach used in patients with a single disease. Yet, recent large randomized controlled trials (RCT) over the last five years have provided important new evidence showing that nutritional support can reduce morbidity and other complications in polymorbid patients, which may help us to answer these question and formulate evidence-based recommendations [8,9].

Polymorbidity is highly prevalent, affecting more than 70% of the hospitalized adult population, and is associated with higher mortality and healthcare burden [10]. Other consequences of polymorbidity include disability, functional decline, poor quality of life (QoL) and higher healthcare costs [5]. Whilst the prevalence increases with age, more than half of all people affected with this problem are younger than 65 years [11]. In this context, the current single-disease healthcare approach has been challenged, as clinical guidelines are largely created for individual diseases and rarely account for polymorbidity [11]. Fried et al. showed that clinicians struggle with the uncertainties of applying disease-specific guidelines to their patients with multiple conditions, and would therefore benefit from a number of tools to assist them in decision making for this population [12]. Limited, if any, accounting for polymorbidity applies to current nutritional guidelines that focus on single diseases (e.g. nutritional support in renal failure) or on patient groups (e.g. older adults). To date, it is unknown whether there is a synergistic negative effect of several diseases on nutritional status, or on clinical outcome. Therefore, there is a need for an updated evidence-based consensus on how to provide nutritional support for the

polymorbid medical inpatient population and to strengthen recommendations that now have a solid evidence base.

2. Materials and methods

2.1. Pragmatic definition of polymorbidity for the current project

This guideline is based on clinical trials that investigate the effects of nutritional support on different outcomes. Because these population-based trials usually report an average number of comorbidities or number of drugs/medications, a pragmatic definition of the polymorbid medical inpatient population was established and does not differ from the original guideline.

- at least two co-occurring chronic diseases present in at least 50% of the study population (in a few of the studies it is stated that x % of the study population suffers from disease A, y% of the study population suffers from disease B, and so on)

or, alternatively,

- a Charlson comorbidity index in the study population as being more than 1.5
- a mean number of diseases or drugs (medications) over 1.5

Polypharmacy is considered to be an important and acceptable marker of polymorbidity, with polypharmacy and polymorbidity having been described as being "two sides of the same coin" [13]. Additionally, it has been shown that the greater the number of medications, the higher the risk of weight loss and manifest malnutrition, which suggests that polypharmacy has a potentially negative effect on nutritional status. The Charlson comorbidity index is the most extensively studied comorbidity index and is considered a valid and reliable method to measure comorbidity that can be used in clinical research [6,14].

In cases of uncertainty about the way that comorbidities were reported, the study authors were contacted in order to obtain additional information. In the event that they could not be reached, a blinded consensus decision within the guideline WG was taken about whether or not to include the study. Some of the included studies were conducted in older populations, since many polymorbid patients are also of an older age. For each included study, the criteria used to consider the study population as being polymorbid was recorded (and reported in the evidence table, in appendix 1).

However, the rigorous methodical approach used came up with some limitations regarding selecting trials and has led to a lower number of included trials. Thus it guarantees that our findings are valid for the population of polymorbid medical inpatients.

2.2. Guideline development

We conducted the update of the guideline with a multidisciplinary team of 14 European specialist in nutritional support from which twelve have already been authors of the original paper from 2018 following the SOP for the development of ESPEN guidelines [2]. The WG decided to keep the previously defined clinical questions as well as the inclusion and exclusion criteria (Table 1). Most of the relevant clinical topics are covered by twelve questions in the PICO format (indication, route of feeding, energy and protein requirements, micronutrients requirements, disease-specific nutrients, timing, monitoring and procedure of intervention). However three topics of interest could not be developed as a PICO-question (underlying disease, polypharmacy and treatment response). The previous question b (duration of intervention) is now incorporated into recommendations 20 to 23 (continued support).

The same search strategies used in the original guidelines were used in the literature searches in 2022. Similar to the original guideline, a systematic literature search was conducted, first in secondary sources by searching published guidelines and systematic reviews potentially relevant for each question, followed by a search in primary sources. On the 12th of July the primary source search update was conducted by the same author in three databases (Medline, Embase and the Cochrane Library) since April 2016.

For all questions, the results from each database were combined and exported to Endnote, followed by removal of duplicates. The abstracts were screened by either one of two WG members in a standardized and systematic way – potential studies (full texts) were then reviewed by both members. Discrepancies were resolved through consensus or recourse to a third review author.

Many studies required the assessment of the full paper to ascertain whether it met all of the inclusion criteria, and for a proportion of the papers (n = 16), the authors were contacted and requested to provide more information, which was usually to clarify whether their study population suffered from multiple

Table 1
Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Patients characteristics	- Human adults aged ≥18 years - Patients hospitalized in acute care wards	- Non human, ≤18 years, pregnant women - Patients admitted to critical/intensive care units - Surgical patients - Patients living on long-term care facilities - Outpatients - Patients receiving end of life care
	- Polymorbid inpatients population as defined by a) at least two co-occurring chronic diseases are present in at least 50% of the study population or b) mean number of diseases or drugs/medication or the Charlson comorbidity index in the study population as being more than 1.5 In case of uncertainties about the way comorbidities are reported, the trials' authors are contacted in order to get more information; if contact is not possible, the WG makes a consensus decision about the inclusion/exclusion of the studies.	- Healthy population - Less than 50% of the study population has two co-occurring diseases
Outcomes	Nutritional outcomes (e.g. weight, energy and protein intake) Clinical outcomes (e.g. mortality, infections) Patient-centered outcomes (e.g. quality of life) Healthcare resources	
Language and year	English; no restriction on publication year	

comorbidities. For those studies whose authors could not be reached (n = 11), seven were included and four excluded, according to the WG consensus decision.

Each WG member was allocated with one or two clinical questions and was responsible for: validation of the literature, quality assessment and assignment of level of evidence for each paper relevant for the recommendations (e.g. using SIGN checklists), generation of first draft of recommendations, including the supporting text and grade of recommendation. The classification of the literature into levels of evidence and grades of recommendation were performed according to the SIGN grading system [15], as exemplified in Tables 2 and 3.

In the original guideline from 2018 a total of 4532 abstracts were screened, 38 relevant studies were analyzed and used to generate a guideline draft that proposed 22 recommendations and four statements. The search update in July 2022 identified 4234 additional possible eligible abstracts; after removing the duplicates, a number of 3527 abstracts were screened. The details of the search update can be found in Table 4. As a result of the update and the conversion of the statements to recommendations, a total of 100 studies are now included.

An evidence table with the number of studies allocated to each question, study details, evidence of polymorbidity for each study population, study type and level of evidence is presented in Appendix 1 (supplementary data: evidence table). These studies can also be identified in the present document through the assignment of the respective evidence level in the text below each recommendation, in bold, e.g. **Level of evidence 2+**.

The WG generated a guideline draft with a total of 32 recommendations (approved by the WG and the ESPEN Guidelines Editorial Board office, which was followed by the start of the consensus procedure, by sending that draft to the members of the ESPEN guideline project, ESPEN members and other experts in clinical nutrition for online voting (Delphi method) in April 2023. The results of this online voting were a strong consensus (agreement of >90%) in 100% of recommendations, which is so far unique in ESPEN guideline development. Nevertheless the feedback received during the online voting was used to make minor changes and improvements to recommendations and supportive text. Due to the large agreement on the first vote, no final consensus conference took place.

3. Results

Question 1. Does nutritional support based on screening and/or assessment versus no screening and/or assessment improve outcomes in polymorbid medical inpatients?

Table 2
Levels of evidence (SIGN grading system) [15].

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

3.1. Recommendation 1

In polymorbid medical inpatients, a quick and simple nutritional screening method using a validated tool should be applied to identify malnutrition risk.

Grade of recommendation B – Strong consensus 97% agreement.

Commentary

Polymorbid medical inpatients are at high risk of malnutrition. Several prospective cohort studies showed a prevalence of approximately 40–50% in a hospitalized population of tertiary centers [16,17]. Observational studies have shown the frequency of complications in untreated at-risk patients to be three times higher than in patients not at-risk, and furthermore length of hospital stay (LOS) is 50% longer, which has a negative influence on clinical outcomes [18]. Further, in the one-day cross-sectional study of Beck et al. patients at nutritional risk were more likely to be readmitted within 30 days (45% vs. 27%, $p = 0.024$) and had a higher mortality within 30 days after discharge (23% vs. 10%., $p = 0.0285$) [19]. Also, in a prospective observational cohort study, Lengfelder et al. were able to show higher odds for malnourished patients having a LOS of ≥3 days (2.38, 95% CI, 1.45 to 3.88; $p < 0.001$) and for readmission within 30 days (2.28, 95% CI, 1.26 to 4.12; $p < 0.006$) [20]. The same effect was shown by Li et al. in patients with community acquired pneumonia [21] **(Level of Evidence 2-)**. The latter also showed a significant increase in the prevalence of nutritional risk measured by the Nutritional Risk Screening 2002 (NRS 2002) within two weeks after admission (40.61% vs. 48.93%; $p = 0.036$).

Scoring systems for determining nutritional risk, such as NRS 2002 and the Mini Nutritional Assessment Short-Form (MNA-SF) link nutritional risk assessment to treatment by predicting that nutritional interventions will have a positive influence on variable outcomes [22–25]. Both of these tools are rapid, easily undertaken and show a high degree of content validity and reliability, thereby making them suitable in polymorbid medical inpatients including those patients with cognitive dysfunction [26,27].

In a secondary analysis of the multicenter, randomized clinical EFFORT trial [8], Stalder et al. investigated the ability of five different nutrition screening and partly also assessment instruments (NRS 2002 [22], Subjective Global Assessment (SGA) [28], Short Nutritional Assessment Questionnaire (SNAQ) [29], MNA-SF [24] and Malnutrition Universal Screening Tool (MUST) [30]) to predict 1-year mortality and response to nutritional treatment. While high nutritional risk was associated with higher mortality in all tools, SGA and MNA-SF showed the strongest association with adjusted odds ratios of 3.17 (95% CI, 2.18 to 4.61, $p < 0.001$) and 3.45 (95% CI, 2.28 to 5.22, $p < 0.001$). When comparing mortality in intervention group (IG) patients to the control group (CG) stratified by severity of malnutrition, there was overall no clear trend towards more benefit in patients with more severe malnutrition, with NRS 2002 and SGA showing the most pronounced relationship between the severity of malnutrition and reduction in mortality as a response to nutritional support [31].

3.2. Recommendation 2

In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to allow an early adequate nutritional therapy and to define quality outcome measures.

Grade of recommendation B – Strong consensus 97% agreement.

Commentary

If patients screen positive, diagnosis should be established according to GLIM criteria – the Global Leadership Initiative on Malnutrition (GLIM) proposes a two-step approach for the malnutrition diagnosis, which includes a validated screening and second, a

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

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

Table 4
Number of abstracts retrieved for each question, in each database, and number of studies included for analysis (original and updated searches).

	Number of abstracts found in the updated searches (2022):				Previous included studies	Total included studies (2016 + 2022)
	Medline	Embase	Cochrane Library	Total (without duplicates)		
Question 1	159	8	271	421	2	3
Question 2	217	274	186	494	11	21
Question 3	159	236	76	357	1	1
Question 4	15	13	0	19	1	2
Question 5	14	14	141	156	2	5
Question 6	23	95	58	161	0	0
Question 7	66	92	176	282	2	4
Question 8	270	259	252	576	2	6
Question 9	4	3	240	238	10	24
Question 10	76	288	245	542	2	5
Question 11	6	8	112	120	2	6
Question 12	30	34	114	161	3	7
Total				**3527**	**38**	**84**
Question 13					2	10
Question 14					0	0
Question 15					0	6
Total						**100**

detailed assessment with phenotypic and etiologic criteria for diagnosis and grading the severity of malnutrition [32]. This guideline did not focus specifically on the assessment and diagnosis with GLIM criteria in polymorbid medical inpatients but generally on assessments to identify pathogenic factors which should be used to develop a treatment plan. The effectiveness of the care plan should be measured by a subsequent monitoring including dietary intake, body weight, and measurements of mental and physical function and of clinical outcome.

In a controlled trial, Rypkema et al. demonstrated that a standardized, early nutritional intervention in older polymorbid medical inpatients at nutritional risk, determined by the MNA-SF, is effective and does not significantly increase hospital costs. The intervention resulted in both a more pronounced weight gain (0.92 ± 0.27 kg in the IG (IG) vs. −0.76 ± 0.28 kg in the CG, $p < 0.001$) and a significant lower rate of nosocomial infections (23.6% vs. 36.7%, $p = 0.01$) **(Level of evidence 2+)**.

In a prospective, non-randomized cohort study, Jie et al. found nutritional support was beneficial for polymorbid medical inpatients at nutritional risk as defined by the NRS 2002 [17] **(Level of evidence 2+)**. The overall complication rate was significantly lower in the group with nutritional therapy than in the no-support group (20.3% vs. 28.1%, $p = 0.009$), primarily because of the lower rate of infectious complications (10.5% vs. 18.9%, $p < 0.001$). These effects were robust after multivariate adjustment. Also, in the same study, the effects of each medical nutrition therapy were analyzed separately, and significantly lower complication rates were found only in patients who received enteral nutrition (EN) compared to the group without nutritional support (8.2% vs. 28.1%, $p < 0.001$).

Question 2. In polymorbid medical inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements, with or without nutritional counseling, versus no oral nutritional supplements, improve outcomes?

3.3. Recommendation 3

In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely receive oral nutrition, individualized provision of nutritional support via oral nutritional supplements (ONS) to reach energy and protein requirements shall be offered to improve their nutritional status, QoL and overall survival.

Grade of recommendation A − Strong consensus 100% agreement.

Commentary

Provision of ONS in acutely ill hospitalized patients or inpatients at risk of developing malnutrition has been found to improve

nutritional intake in terms of energy and protein and have a positive impact on nutritional status, clinical outcomes and overall survival. Hegerová el al. conducted a prospective RCT in 200 inpatients from an internal medicine department and found that the provision of ONS (combined with physiotherapy) increased the overall nutritional intake, mainly energy (1954 ± 429 kcal in the IG vs. 1401 ± 364 kcal, $p < 0.001$) and protein (76.3 in the IG ±16.1 vs. 55.5 in the CG ±13.7, $p < 0.001$), without negatively affecting the hospital food consumption (72.8% in the IG vs. 71.3% in the CG, $p = 0.528$) [33] **(Level of evidence 1++).** This supplementation resulted in significant preservation of muscle mass (lean body mass difference between admission and three months after discharge was −3.5 kg in CG patients, and +1.3 in the IG) and independence (the difference in the Barthel Index (BI) values between admission and three months showed a statistically significant decline in the CG ($p < 0.01$) vs. a non-significant decline in the IG). Therefore, ONS have a supplemental role in the provision of nutrition during hospitalization. Schuetz el al., in the EFFORT trial, reported a lower risk of adverse clinical outcome in the IG compared to controls (adjusted OR 0.79, 95% CI 0.64 to 0.97, $p = 0.023$) and a lower risk of mortality (adjusted OR 0.65, 95% CI 0.47 to 0.91, $p = 0.011$), with no statistically significant difference in side effects between both groups [34] **(Level of evidence 1++). Similarly,** improved survival in medical inpatients receiving nutritional support was reported in the meta-analysis by Gomes et al. where the analysis of 27 trials resulted in lower mortality rates in patients receiving nutritional care vs. the controls (230 of 2758 [8.3%] vs. 307 of 2787 [11.0%]; OR 0.73; 95% CI, 0.56–0.97) [35]. Nutrition support was also associated with lower non-elective hospitalizations 14.7% vs. 18.0%; RR 0.76; 95% CI 0.60 to 0.96) improved energy and protein intake (mean difference of 365 kcal, 95% CI 272–458 kcal for energy and mean difference of 17.7 g, 95% CI 12.1–23.3 g for protein), and improvements in nutritional and functional status **(Level of evidence 1++).** A meta-analysis by Gressies et al. conducted in 2022 that was an update and re-analysis of Gomes et al. included trials exclusively conducted within the population of polymorbid patients using the exact same definition as used in this guideline. The analysis showed again a significant reduction in mortality risk (OR 0.68; 95% CI 0.51–0.91) (Fig. 1) and hospital readmissions (OR 0.64; 95% CI 0.45–0.90) proofing the effectiveness of nutritional support in this vulnerable patient group with complex combinations of diagnoses [36] (**Level of evidence 1++**).

The long-term effects of individualized nutritional support during hospitalization are also of interest. According to a secondary analysis of the EFFORT trial by Kaegi-Braun et al., the positive effects of individualized nutritional support provided during hospitalization which were observed at 30 days, were not sustained at six months after discharge when nutrition was not continued [37] **(Level of evidence 1++**). Therefore, the effect of long-term provision of individualized nutritional support continuing as homecare should be a subject of future research.

3.4. Recommendation 4

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, high protein nutrient specific ONS should be administered, when they may help maintain functional status and muscle mass, reduce mortality and improve QoL.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary

Several nutrient specific ONS have been tested for their effectiveness on the improvement of outcomes in hospitalized patients. High protein ONS containing – β-Hydroxy β-Methylbutyrate (βHMB) have been tested for their effect on muscle mass and functionality. According to the NOURISH study, a multicenter RCT which included 652 malnourished inpatients, high protein βHMB ONS may not yield a difference when compared with placebo on readmission rates, but may help with the maintenance of muscle mass during hospital stay and result in a significant decrease in post-discharge mortality (90-day mortality was 4.8% in the IG vs. 9.7% in the CG; RR 0.49, 95% CI 0.27 to 0.90, $p = 0.018$) [9] **(Level of evidence 1++).** The effects of this ONS were also positive in a subgroup of patients with chronic obstructive pulmonary disease (COPD) from the same study, where the IG had significant decreased mortality risk compared to the CG (1.83%, 2.75%, 2.75% vs. 6.67%, 9.52% and 10.48%, $p = 0.0395$, 0.0193, 0.0113, respectively). Moreover, COPD patients receiving the high protein βHMB ONS showed an increase in handgrip strength (HGS) from discharge to 30 days (1.56 kg vs. −0.34 kg, $p = 0.0413$) and increased body weight (0.66 kg vs. −0.01 kg, $p < 0.05$) [38] **(Level of evidence 1++).** Improved functionality measured by HGS was also observed in other subgroup analyses from the NOURISH study, including patients with cardiovascular and pulmonary disease. Patients receiving specialized ONS showed in a greater extent improvement in HGS, nutritional and performance status, compared to the controls receiving the placebo ONS (49% vs. 31%, $p = 0.0003$) [39] **(Level of evidence 1++).**

In addition, provision of ONS containing 995 kcal from macronutrients and covering 100% of the RDA for healthy older adults in vitamins and minerals led to a lower incidence of depressive symptoms ($p = 0.021$) in older medical inpatients, with no other

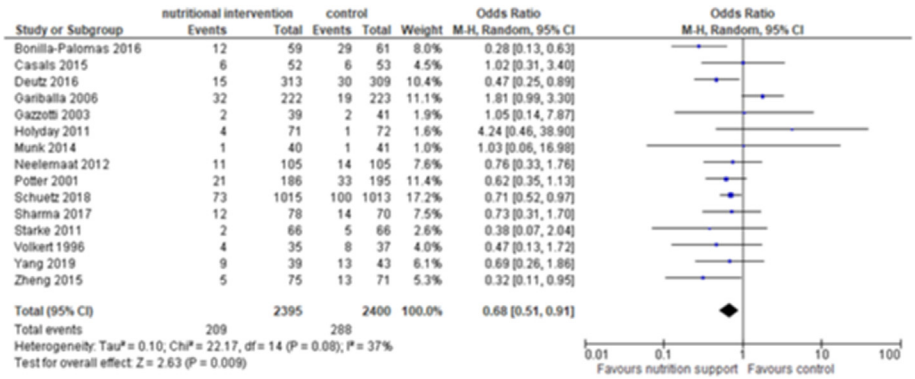

Fig. 1. Forest plot comparing nutritional intervention versus control for mortality in polymorbid medical inpatients [36].A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95% CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95% CIs. OR indicates odds ratio.

effect on their cognitive performance but with a significant positive effect on their self-reported QoL (i.e. the treatment effect in QoL scores using the SF-36 form at 6 months was 7.0, 95% CI 0.5 to 13.6, p = 0.04 for physical function, 10.2, 95% CI 0.1 to 20.2, p = 0.047 for role physical, and 7.8, 95% CI 0.0 to 15.5, p = 0.05 for social function domains, compared to placebo) [40,41] **(Level of evidence 1++ for both).**

Wound-specific ONS have also been tested for their effectiveness in polymorbid patients during rehabilitation. A supportive retrospective analysis of data collected from 341 patients showed that the daily provision of wound-specific ONS resulted in a significant greater decrease in the wound area, compared to the patients who did not receive nutritional support (61.1% in the IG vs. 34.5% in the CG, p = 0.01) [42]. Although these results are interesting and promising, the available studies remain limited.

3.5. Recommendation 5

In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely receive nutrition orally, ONS shall be offered as a cost-effective way of intervention towards improved outcomes.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Early detection and intervention against DRM has been shown to improve nutritional status and reduce complications during hospital stay and non-elective readmissions [9,43] **(Level of Evidence 1++ for both).** According to a cost-effectiveness analysis by Philipson et al., in a retrospective study from 2000 to 2010, the provision of ONS to malnourished medical inpatients resulted in a reduction in LOS of 2.3 days, 95% CI -2.42 to −2.16 that subsequently decreased annual hospital costs by 4734 $, 95% CI -4754 $ to −4714 $, and reduced the readmission rate by 6.7%, from 34.3% to 32.0% [44] **(Level of evidence 2++).** The greatest benefit was recorded in the most severely ill patients, which was a finding in general agreement with the "Feed Or Ordinary Diet" multi-center RCT, in which routine ONS (independent of baseline nutritional status) did not offer significant benefits to a mostly well-nourished stroke patient population (OR of death or poor outcome was 1.03, 95% CI 0.91 to 1.17 for the overall group and 0.78, 95% CI 0.46 to 1.35 in the small undernourished subgroup). This stresses the importance of providing nutritional support to those most in need [45] **(Level of Evidence 1++).**

The cost analysis of the multicenter, randomized clinical EFFORT trial showed that nutritional support for polymorbid medical inpatients is a highly cost-effective intervention to reduce risks for ICU admissions and hospital-associated complications, while improving patient survival. Overall costs of care within 30 days of admission averaged 27,240 € per-patient in the IG versus 27,439 € in the CG resulting in per-patient cost savings of 199 €. The economic benefits calculated to prevent adverse outcomes were 256 € for one severe complication, 2490 € for one day in ICU, and 7423 € for one death [46] **(Level of Evidence 2+).**

For polymorbid medical inpatients who are malnourished or at nutritional risk, the economic analysis using modelled cost-savings calculations of several RCTs reflect reductions in infectious complications, LOS, and non-elective readmissions, as measures for the effectiveness of in-hospital nutritional support. In the meta-analysis of Schuetz et al. the overall costs of care within the model timeframe of 6 months averaged 63,227 $ per patient in the IG vs. 66,045 $ in the CG, which correlate to per patient cost savings of 2818 $. These cost benefits were mostly due to reduced infection rates and shorter lengths of stay. The authors also calculated 820 $ to prevent a hospital-acquired infection and 733 $ to avoid a non-elective readmission [47].

Positive results were also reported in a meta-analysis of RCTs on hospitalized patients at high risk of developing pressure ulcers, by Tuffaha et al. Provision of nutritional support resulted in a cost saving of 425 $ per patient and a marginal improvement of quality adjusted life years of 0.005, compared to the usual care [48] **(Level of evidence 1++).**

Regarding the provision of nutrient specific ONS, Zhong et al. conducted an economic evaluation of NOURISH study. According to this analysis the provision of high protein βHMB ONS had an incremental cost-effectiveness ratio (ICER) of 524 $/life years, concluding that this intervention was cost effective and positive in terms of survival for the patients [49] **(Level of Evidence 1++).** Moreover, a similar analysis was conducted by Ballesteros-Pomar et al. from the perspective of the Spanish National Health System in the patients included in NOURISH study. According to their analysis the intervention proved to be cost effective, improved survival and marginally reduced cost of treatment [50] **(Level of evidence 1+).**

Question 3. In patients where nutritional requirements cannot be met orally, does the use of enteral nutrition compared to parenteral nutrition (total or supplemental) result in improved outcomes in polymorbid medical inpatients?

3.6. Recommendation 6

In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN before parenteral nutrition (PN) can be administered to ensure reaching nutritional goals.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

Reaching energy goals in medical inpatients is important to prevent weight loss and the loss of muscle mass that may lead to poorer functional outcomes. However, in the acute care setting many obstacles may prevent patients from meeting their nutritional requirements orally. These obstacles include loss of appetite due to acute illness, delayed gastric emptying causing both nausea and early satiety, inability to swallow, and vomiting, among others. In these situations, use of EN or PN can help increase nutritional intake until oral intake is sufficient [51,52]. Several randomized studies have compared the effect of nutritional support on outcomes of medical inpatients. A 2019 systematic review and meta-analysis on nutritional support in medical inpatients found significantly improved clinical outcomes in those receiving adequate nutritional support. The review included 27 RCTs from several countries comprising 6803 medical inpatients, and reported a 27% reduction in mortality and non-elective hospital readmissions [35]. The review also found significantly higher energy and protein intake, as well as beneficial effects on weight when comparing nutritional support (including counseling and oral and enteral feeding) to CG patients.

3.7. Recommendation 7

In polymorbid medical inpatients whose nutritional requirements cannot be met orally, the use of EN may be superior to PN because of a lower risk of infectious, non-infectious complications and maintenance of gut integrity.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

Several studies are using nutritional strategies typically providing a combination of oral nutrition, EN and/or PN compared to usual care or other feeding strategies in the medical inpatient setting [53–55]; these studies, however, did not directly compare the two feeding modalities. There are also several studies that investigated whether EN compared to PN resulted in better outcomes. While most studies examined the critical care setting and patients with acute pancreatitis [56–58], there is some observational evidence for the polymorbid medical inpatient population [17]. This observational evidence consists of one large, prospective, non-randomized study (briefly described in the clinical question 1) from three institutions in the US and China including patients at nutritional risk, as defined by the NRS 2002, that investigated the outcomes of patients receiving either EN or PN to patients without nutritional support [17] (**Level of evidence: 2+**). Approximately two thirds of the patients were medical patients from the department in respiratory and gastrointestinal diseases. Because the study was non-randomized, the authors used multiple logistic regression analysis to evaluate the influence of nutritional support on the risk of infectious and non-infectious complications. Overall, the study found a significantly lower risk of overall complications and infectious complications associated with nutritional support (adjusted OR 0.54, 95% CI 0.38 to 0.77), $p < 0.001$ and adjusted OR 0.42, 95% CI 0.27 to 0.64, $p < 0.001$, respectively). When the nutritional support group was further divided into those receiving PN and those receiving EN, the overall complication rate and the rates of infectious complications and non-infectious complications were significantly lower in those patients receiving EN than in those patients with no nutritional support ($p = 0.001$). However, no difference in the complication rates was found between patients with PN and patients with no nutritional support ($p = 0.29$). Because of differences in the patient population, this analysis was also repeated in patients undergoing major abdominal surgery who had PN or no nutritional support. Again, no significant difference in the complication rate was found between PN patients and control patients. This study has a number of important limitations regarding the observational, non-randomized design with important differences in study populations between PN and EN patients (as well as no-nutritional support patients), differences in hospital characteristics between the Chinese and US hospitals and the lack of a standardized follow-up. Thus, causal inferences cannot be drawn. Still, the study suggests that EN may be more beneficial than PN, due to fewer infectious and non-infectious complications.

Albeit outside the scope of these guidelines, studies from critical care demonstrated that EN compared to PN results in similar mortality but lower complication risk. Specifically, a recent meta-analysis of 18 RCTs studying 3347 patients did not find benefits in terms of mortality. In that meta-analysis, EN compared to PN was associated with a significant reduction in infectious complications (RR 0.64, 95% CI 0.48 to 0.87, $p = 0.004$) and with a significant reduction in ICU LOS (weighted mean difference [WMD] −0.80, 95% CI -1.23 to −0.37, $p = 0.0003$, $I^2 = 0\%$), while no significant differences in hospital LOS and mechanical ventilation were observed. Authors stated that these results may be explained by the benefit of reduced macronutrient intake (avoidance of overfeeding) rather than the enteral route itself [59]. Similarly for pancreatitis, a meta-analysis including eleven trials and 562 patients found that compared with PN, EN was associated with decreased mortality (relative risk 0.43, 95% CI 0.23 to 0.78, $p = 0.006$), a lower risk of infection and complications (RR 0.53, 95% CI 0.39 to 0.71, $p = 0.000$) and a reduction in mean LOS (mean difference = −2.93, 95% CI -4.52 to −1.34, $p = 0.000$) [60].

In summary, several trials found that the addition of either EN or PN to oral nutrition improves outcomes, but high-quality randomized studies comparing EN and PN head-to-head in the polymorbid medical inpatient setting are scarce. Still, when also considering high-quality evidence from critical care and in patients with pancreatitis as well as observational evidence from polymorbid medical inpatients, there are several arguments for the use of EN as a first line therapy as compared to PN due to lower risks for infectious and non-infectious complications. A physiological rational is also the prevention of intestinal mucosal atrophy by EN compared to PN [61].

Question 4. Does the estimation of energy requirements with a prediction equation versus a weight-based formula improve outcomes of polymorbid medical inpatients requiring nutritional support?

3.8. Recommendation 8

Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula, although the accuracy of prediction equations in this population is low.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary

The estimation of energy requirements is an important part of the patient assessment process and requires the determination of an individual's total energy expenditure (TEE) i.e. the sum of resting energy expenditure (REE), diet-induced thermogenesis and the energy expended during physical activity. The gold standard to measure REE is IC and for TEE the gold standard is doubly labelled water. However, these methods are rarely available in the clinical setting (almost never for the latter) and require considerable expertise [62]. Practitioners therefore tend to rely on either published prediction equations (e.g. Harris-Benedict [63] or Ireton-Jones [64]) or weight-based formulae (e.g. 25–30 kcal/kg body weight), to estimate energy requirements. In prediction equations, energy requirements are estimated from a number of different parameters e.g. weight, age, gender, ventilation status, heart rate etc.; in weight-based formulae the prediction is based solely on patient body weight. No single, validated method for estimating requirements exists, and the evidence-base for all prediction methods currently in use is poor [65]. In the absence of IC, there is a debate about which of the two estimation methods is the most valid for use in the clinical setting. However, no studies were identified that answered this specific question.

While both published prediction equations and weight-based formulae provide valid estimates of energy requirements for groups of patients, both methods are subject to significant bias and imprecision when applied to individuals [66,67]. More than 200 prediction equations have been published in the literature, with accuracy rates ranging from 36% to 75% when compared with IC and no single equation emerges as being the most accurate in polymorbid medical inpatients [66]. Practitioners should therefore exercise a considerable degree of clinical judgment when determining the energy requirements of a polymorbid medical inpatient.

This also includes the choice of activity or stress factors, which relies on the clinical judgment, knowledge, and experience of the individual calculating the predicted requirements − it should be undertaken with caution since their misapplication can lead to clinically significant errors.

Individuals requiring nutritional support range from paralyzed and sedated, critically ill patients to fully mobile patients on the ward or in the community. To date, however, there is a relative lack of research on the effects of illness and injury on physical activity levels, although a recent consensus document concluded that since

acute illness is usually accompanied by a decrease in physical activity that compensates for any increase in BMR, TEE is rarely above that of healthy, sedentary individuals of the same sex and age [68]. In a study designed to evaluate the accuracy of prediction equations against IC in hospitalized patients, REE was measured by IC in 395 inpatients referred for nutritional support. REE measurements were compared with three prediction equations including one specifically for obese individuals [63,64,69] and one weight-based formula recommended by the American College of Chest Physicians (25 kcal/kg body weight). The mean age of the population was 56 ± 18 years and the mean BMI was 24 ± 5.6 kg/m^2. Measured REE was 1617 ± 355 kcal/day for the entire group and 1790 ± 397 kcal/day in the obese group (n = 51). In this study the authors concluded that no single prediction equation was accurate (i.e. within 90–110% of measured REE) in the majority of the population. Another recent study conducted in 23 malnourished polymorbid, older hospitalized patients (mean age of 81.8 ± 8.1 years and mean BMI of 23.4 ± 4.0 kg/m^2) confirmed these results: the average REE predicted by the Harris–Benedict formula exceeded the REE measured by IC (after an overnight fast) on admission and at discharge by 29% and 11%, respectively, suggesting that the Harris–Benedict formula is not accurate in this patient population [70] **(Level of evidence 2+)**.

Clinicians should be aware of the limitations of using precise numbers on weight-based formulae (or prediction equations) since in all studies there is considerable variation around the effect estimate. They should recognize that all prediction methods are imprecise when applied to individuals and therefore should only be used as a starting point when estimating requirements. In fact, this highlights the need for input from a suitable and experienced healthcare professional to adequately assess the nutritional needs of the patient, e.g. a dietitian.

3.9. Recommendation 9

In the absence of IC, TEE for polymorbid older patients (aged ≥65 years) can be estimated at approximately 27 kcal/kg actual body weight/day. REE can be estimated at 18–20 kcal/kg actual body weight/day with the addition of activity or stress factors to estimate TEE.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

In a review designed to determine the energy requirements of frail older people [71], including polymorbid patients, 33 studies (2450 subjects) were identified where REE was measured by IC in subjects aged 65 years or more and the results were compared with healthy older individuals **(Level of evidence 2++)**. Only studies that measured REE by IC after a fast and at rest were considered eligible for inclusion in the review. The mean age was 73.0 ± 6.6 years, with no significant difference in BMI between the healthy and sick cohorts (25.6 ± 1.5 kg/m^2 and 25.2 ± 2.5 kg/m^2 respectively) and no differences in fat mass or fat-free mass. The weighted mean for the whole group was 20.4 kcal/kg actual body weight whereas the weighted mean for the polymorbid hospitalized older group was lower at 18.5 kcal/kg body weight. The mean TEE in sick older individuals was 27 ± 1.8 kcal/kg body weight and the weighted physical activity level in these patients was 1.36 ± 0.03 reflecting the relative physical inactivity of this population. The results of this review should be interpreted with caution since relatively few data were available in the sick older individuals (n = 248) compared with the healthy older individuals (n = 1970). Furthermore the methods described in the paper failed to comply fully with guidelines for the conduct of systematic reviews [72]. For example, only one database (MEDLINE) was searched when it is recommended that at least three should be searched, and only studies published in English were included.

3.10. Recommendation 10

In the absence of IC, REE for severely underweight patients can be estimated at 30 kcal/kg actual body weight.

Grade of recommendation 0 – Strong consensus 96% agreement.

3.11. Recommendation 11

This target of 30 kcal/kg actual body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary

In a study designed to determine the energy requirements of severely underweight hospitalized patients energy expenditure was measured by IC in 14 patients [73]. Mean BMI was 15.8 ± 1.8 kg/m^2 and mean age was 66.5 ± 13.9 years. In this study mean REE by IC was 1300 ± 160 kcal/day equating to 31.4 kcal/kg body weight. These results should be interpreted with caution since the sample size was very small. Furthermore, patients received continuous EN or PN during IC and thus measured energy expenditure included not only REE but also diet-induced thermogenesis.

The target of approximately 30 kcal/kg body weight in severely underweight patients may need to be achieved with caution, as this is a population at high risk of refeeding syndrome. The diagnostic criteria and the factors proposed for screening of refeeding syndrome have been proposed elsewhere [74].

From the review of the literature, it is not possible to determine which method of estimating energy requirements (or which prediction equation) is the best in terms of promoting better outcomes in the polymorbid medical inpatient population.

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation 11 is limited to the subgroup of polymorbid older patients. For further information regarding the nutritional care of older patients, please refer to the existing ESPEN guidelines on clinical nutrition and hydration in Geriatrics [75].

Question 5. Do protein targets higher than 1.0 g/kg body weight/day versus a lower target improve outcomes in polymorbid medical inpatients requiring nutritional support?

3.12. Recommendation 12

Polymorbid medical inpatients requiring nutritional support shall receive 1.2–1.5 g protein/kg of body weight per day as a cost-effective and highly efficient measure to prevent body weight loss, to reduce complications, to improve functional outcome and QoL.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Protein targets of at least 1.0 g/kg body weight have been recommended in the past [1], e.g. supported by a high-quality RCT with 132 polymorbid patients (**Level of evidence 1++**). More recent and larger RCTs, such as the EFFORT trial (**Level of Evidence 1++**) including 2028 polymorbid patients, support a higher daily protein target of 1.2–1.5 g/kg body weight [8,37,46]. Compared to the usual care CG, odds for adverse outcomes and 30-day mortality were significantly lower in patients receiving individualized nutrition with these protein targets (OR 0.79, 95% CI 0.64 to 0.97

and OR 0.65, 95% CI 0.47 to 0.91 respectively), while functional status via BI, and QoL significantly increased. An economic evaluation of EFFORT indicates that the high-protein nutritional support was highly cost-effective with per-patients savings of 199 € of overall costs of care within 30 days of admission; and 18 € in full cost analysis (**Level of Evidence 1**++) [46].

To reach high protein targets of 1.2–1.5 g/kg body weight, several strategies were used in the trials and interchangeably combined to respect patients individual preferences including ONS, protein-rich hospital menu, food fortification, and high-protein deserts and snacks [8,76,77].

The results of a recent meta-analysis from 2021 demonstrated that high protein intake was one of the strongest predictors for beneficial mortality effects of nutritional interventions: trials using high-protein strategies in medical inpatients at nutritional risk, had significantly stronger effects on mortality compared to trials with low-protein interventions (OR 0.57, 95% CI 0.44 to 0.74 vs. 0.93, 95% CI 0.73 to 1.19). High-protein interventions were considered when ONS with more than 20% protein were used or individual protein goals above 1 g of protein per kilogram body weight was defined [78]. In line with this finding, the recommendations from guideline on nutritional therapy by the American College of Gastroenterology [56] and other expert groups [51,79,80] for older patients and general inpatients are advocating daily protein targets of at least 1.2 g/kg body weight and even higher intake for individuals with severe illness [79].

Regarding combination of nutrition with exercise, several societies recommend to combine high-protein intervention with physical activity, to maintain or enhance muscle mass in malnourished older patients, including the ESPEN guideline for geriatrics and an ESPEN expert group on protein requirements in older adults [75,79]. This combination has been shown effective for the prevention and treatment of sarcopenia in several trials [81–85]. For instance, one RCT of 47 malnourished polymorbid patients participating in a rehabilitation program on a geriatric ward, compared whey supplementation vs. no whey supplementation and demonstrated positive effects on daily protein intake (1.48 vs. 1.05 g/kg body weight) and muscle strength [76] (**Level of Evidence 1**+). Still, there is remaining uncertainty regarding the specific role of exercise in high-protein interventions in the group of polymorbid medical inpatients at nutritional risk, because there is a lack of trials comparing head-to-head protein supplementation with exercise vs. without exercise [76,86,87].

3.13. Recommendation 13

For polymorbid medical inpatients at nutritional risk with impaired kidney function (eGFR <30 ml/min/1.73 m^2) who are not on kidney replacement therapy, a low amount of protein of 0.8 g protein/kg body weight/day should be targeted.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary

In the case of polymorbid medical inpatients with impaired kidney function, protein requirements should be lower [51]. ESPEN Guideline on clinical nutrition for kidney disease recommends setting protein targets preferably guided by protein catabolic rate. Referring to body weight, it is recommended to start with a protein intake of 1 g/kg body weight per day and gradually increase up to 1.3 g/kg body weight for medical inpatients with acute kidney injury (AKI) or chronic kidney disease (CKD) without kidney replacement therapy (KRT). Different recommendations are made for patients with other renal conditions, e.g. 0.6–0.8 g for patients with CKD without acute illness or 1.2 g/kg body weight/day if those patients are on conventional intermittent chronic KRT and higher intakes for critically ill patients [88]. However, those recommendations do not refer specifically to polymorbid patients with kidney diseases.

Within EFFORT [8], protein targets of 1.2–1.5 g were lowered to 0.8 g/kg body weight/day for patients with eGFR <30 ml/min/1.73 m^2 according to earlier guidelines [1,88]. However, the degree of kidney impairment was a strong predictor for response to nutritional support and patients with eGFR of 15–29 l/min/1.73 m^2 receiving 0.8 g and those with 30–59 ml/min/1.73 m^2 receiving 1.2–1.5 g/kg body weight/day showed the strongest benefits on 30-day mortality (OR 0.37, 95% CI 0.14 to 0.95 and 0.39, 95% CI 0.21 to 0.75, respectively) (**Level of Evidence 1**++) [89]. This finding supports the concept of adjusting protein goals in polymorbid patients with renal conditions and impaired kidney function for eGFR and using targets from 0.8 g/kg body weight if eGFR is < 30 ml/min/1.73 m^2 and at 1.2–1.5 g with eGFR if $\geq$ 30 ml/min/1.73 m^2. However, based on our search, there is a lack of trials comparing higher vs. lower protein targets in the polymorbid patient population with impaired kidney function. A recent critical review supported by the European Renal Nutrition Group of the European Renal Association (ERN-ERA) and ESPEN also recommends that renal status be prioritized in patients with advanced CKD (stages 4 and 5) [90]. However, they conclude that patients with CKD need a personalized approach depending on nutritional status and renal condition, and that renal and nutritional priority (protein restriction vs. no protein restriction) may substitute for each other over time.

Question 6. In patients exclusively fed orally, does micronutrient (vitamins and trace elements) supplementation compared to no supplements improve outcomes in polymorbid medical inpatients?

3.14. Recommendation 14

In polymorbid medical inpatients exclusively fed orally, an adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients may be at risk of micronutrient deficiency as a result of decreased intake or greater micronutrient utilization, which can compromise health as well as recovery from illness or disease. Some studies suggest beneficial outcomes from supplementation of micronutrients: for example, a study relating micronutrients to COVID-19 infection by James et al. reported limited evidence that supplementation of certain micronutrients can prevent severe disease or shorten time to recovery [91]. In another study, a Swiss group reported fewer adverse effects in medical inpatients $\geq$18 years outside of intensive care from early implementation of individualized nutrition support goals which included micronutrient provision, although any role the specific micronutrient goal had is unclear [8]. Just as underprovision of micronutrients could compromise polymorbid medical inpatients so too could overprovision. For example, a meta-analysis of mixed study populations found additional micronutrient supplementation to a therapeutic diet [74] already supplemented in micronutrients did not reduce mortality and may have increased LOS by approximately one day (albeit with borderline statistical significance) [92].

General micronutrient supplementation, with or without supplementation of specific micronutrients, based only on the provision of multivitamins rather than a combined multivitamin and multi-trace element appears to be common, and often based on financial cost of the supplement. However, if a subject may have general micronutrient depletion or generally increased

micronutrient requirements then there is likely to be a need to provide trace elements as well as vitamins. Therefore, in the absence of specific toxicity risks or known micronutrient adequacy, supplementation should aim to deliver a complete range of both multivitamins and multi-trace elements rather than multivitamins alone. Complete micronutrient supplementation to meet reference nutrient intakes or otherwise estimated daily requirements could be particularly important in polymorbid medical inpatients due to the potential for any deficiencies to affect multiple and already compromised organ systems. Micronutrient requirements in older adults, frail or unwell subjects are unclear, but these groups may be particularly at risk of deficiencies [75]. ESPEN provides practical advice on micronutrient status affecting disease and vice versa, micronutrient provision and monitoring, and potential micronutrient deficiencies resulting from medicine administration such as vitamin B12 or iron with proton pump inhibitors, or thiamine with diuretic therapy [93]. The mechanisms by which these deficiencies could occur vary according to the medicine and nutrient. No studies were identified that reported the supplementation of multivitamins (with or without trace elements) compared to no supplements in polymorbid medical inpatients exclusively fed orally.

3.15. Recommendation 15

In polymorbid medical inpatients exclusively fed orally, documented or suspected micronutrient deficiencies should be repleted.

Grade of recommendation GPP – Strong consensus 96% agreement.

Commentary

The need for micronutrient supplementation is often based on clinical assessment of the subject and in some cases estimated daily micronutrient requirements may temporarily exceed recommended daily intakes in order to account for depleted stores and/or increased utilization (particularly in patients who are exclusively fed orally). For example, a study by Joosten et al. found hospital inpatients >65 years of age likely to be deficient in vitamin B12, folate and/or vitamin B6, even though the same subjects had apparently normal reported levels of the same micronutrients [94]. A study by Kilonzo et al. [95] on self-reported morbidity from infections in free-living patients (rather than inpatients) aged >65 years, randomized to receive either a daily vitamin and mineral supplement or placebo, found fewer QALYs per person in the supplemented group. This result is counter-intuitive; however, incomplete supplements not designed to replete micronutrient stores were used despite almost one third of the participants being judged at risk of micronutrient deficiency on recruitment. Daily micronutrient supplementation in free living individuals ≥60 years old did not improve incidence and severity of acute respiratory tract infections [96], although since the subjects were well-nourished they perhaps did not benefit from the supplementation. Another study of frail subjects in the community ≥65 years found a reduction in frailty with increased dietary intake but not with supplementation of only micronutrients [97]. However, the potential influence of increased micronutrient intake associated with the higher dietary intake in this study is unclear and the micronutrients-only group received estimated daily needs rather than repletion. Supplementation of some nutrients could affect supplementation of others, although there was no reduction in nutrient intake from food with increased micronutrient intake in those aged ≥65 years consuming high-protein ONS post discharge [98].

Question 7. Does disease-specific nutritional supplementation (e.g. fiber, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard formulations improve outcomes in polymorbid medical inpatients?

Many specialized ONS/EN feeds have been developed for specific diseases that usually involve chronic/acute inflammation, specific micronutrient deficiency or specific metabolic disorders [99]. However, most studies were not conducted in identified hospitalized polymorbid patients, even though some of these patients may well be polymorbid, and the number of useable studies identified is extremely low.

3.16. Recommendation 16

In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and βHMB can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.

Grade of recommendation 0 – Strong consensus 92% agreement.

Commentary

Pressure ulcers are responsible for protein loss, hypermetabolism and hypercatabolism, and are often associated with malnutrition, including nutrient deficiencies that are critical to the different phases of wound healing (conditionally essential amino acids and antioxidant micronutrients). A RCT from Singapore that included 26 polymorbid patients hospitalized for more than two weeks [100] showed a marginal albeit significant effect of an arginine/glutamine/βHMB mixture on the healing of pressure ulcers (greatest improvement of viable tissues at two weeks in the IG, by 43% vs. 26%, $p = 0.02$) **(level of evidence 1+)**. The amino acid mixture (14 g arginine, 14 g glutamine and 2.4 g calcium βHMB per day) was not part of a nutritional formula, but all patients were fed per recommendations for hypermetabolic and hypercatabolic patients (30–35 kcal and 1.2–2.0 g protein/kg body weight/day according to the stage of the ulcer). As the basic nutritional needs were covered in both groups, the supplement (administered orally or enteral) was likely responsible for the beneficial effects observed. In another RCT from Hong Kong, 87 polymorbid malnourished older adults with pressure ulcers were randomized to receive or not the same mix of arginine/glutamine/βHMB for four weeks, besides an adapted nutritional support (at least 30 kcal and 1.2 g protein/kg body weight/day) [101], (**level of evidence 1+**). A statistically significant reduction in pressure ulcer size ($p = 0.048$) and depth ($p = 0.002$) was observed in the IG while the Pressure Ulcer Scale for Healing (PUSH score) showed a significant improvement in the CG ($p < 0.001$). However, there was no between group difference on pressure ulcer healing in term of pressure ulcer area, depth, undermine and PUSH score.

Other positive studies have been published using an oral nutritional supplement enriched in arginine, zinc and antioxidants in patients outside the scope of these guidelines [102,103].

3.17. Recommendation 17

In polymorbid medical older inpatients requiring EN, EN formulas enriched in a mixture of soluble and insoluble fibers can be used to improve bowel function.

Grade of recommendation 0 – Strong consensus 96% agreement.

Commentary

Diarrhea and constipation are the most frequent complications of EN in hospitalized patients. A Belgian study of 145 older patients receiving enteral feeding [104] found positive effects of a formula enriched with 30 g fiber including 33% insoluble (cellulose and hemicellulose A) and 67% soluble (pectin, hemicellulose B, inulin) fiber (IG) vs. the CG, which received the same EN with no fiber **(level of evidence 1++)**. The frequency of stools was lower (4.1 ± 2.6 per week versus 6.3 ± 4.7 per week; $p < 0.001$) and the

stool consistency higher in the IG (31% had solid form stools in the IG vs. 21% in the CG, and 2% had liquid-watery stool in the IG vs. 13% in the CG, $p < 0.001$); however, patients in the CG received more laxatives during the study period than patients in the fiber group. A global 4-week mortality of 24% underlines the severity of the patients' conditions.

The effects on bowel function associated with the absence of detrimental metabolic effect argue for a recommendation for a first intention use of EN formulae enriched with a mixture of soluble and insoluble fibers (supposed to match the multiple sources of fibers in normal food). The same recommendation has been made in ESPEN's clinical nutrition and hydration guidelines in geriatrics [75].

Recommendation 17 was downgraded from grade of recommendation B to 0, due to the limited number of available studies in identified polymorbid medical inpatients**.**

3.18. Recommendation 18

We cannot recommend the use of other disease-specific nutritional supplementation in polymorbid medical inpatients.

Grade of recommendation 0 – Strong consensus 100% agreement.

The scarcity of quality intervention studies in populations adequately described as polymorbid does not allow to recommend the use of other disease-specific nutrients.

One of such prospective studies with negative findings was conducted in Japan in 50 patients with exacerbation of COPD [105] (**Level of evidence 1+**). They were randomized to receive either ONS with 1.1 g of eicosapentaenoic acid (EPA) or a comparable one without n-3 fatty acid during their hospitalization, both groups receiving a total of 30–35 kcal/kg/day. At discharge (after 12–13 days of supplementation in both groups), there was a non-significant increase in lean body mass index and skeletal muscle mass index in the EPA group compared with the CG (lean body mass index: +0.35 vs. +0.19 kg/m^2, $p = 0.60$, and skeletal muscle mass index: +0.2 vs. −0.3 kg/m^2, $p = 0.17$, respectively). The changes in skeletal muscle mass index were significantly correlated with the LOS in the EPA group, but not in the CG ($r = 0.53$, $p = 0.008$, and $r = -0.32$, $p = 0.31$, respectively).

Question 8. Does early nutritional support (i.e. provided less than 48 h post hospital admission) compared to later nutritional support improve outcomes in polymorbid medical inpatients?

3.19. Recommendation 19

Early nutritional support (i.e. provided in less than 48 h post hospital admission) compared to later nutritional support shall be performed in polymorbid medical inpatients, as mortality and adverse events are lower and lean body mass loss could be decreased and self-sufficiency could be improved.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients are at high risk of developing DRM, so it is possible that this population could benefit from early nutritional support during hospital admission to avoid worsening of DRM with subsequent negative outcomes.

The use of early nutritional support is debated in different clinical scenarios and patient populations. From the available literature addressing this question in medical inpatient populations with confirmed polymorbidity, six studies were identified.

The previous described large EFFORT trial [8] addressed this question as the IG got their therapy initiated within 48h. By 30 days, patients in the IG experienced 21% less adverse clinical outcomes and 35% lower mortality (adjusted OR 0.65 [0.47 to 0·91], $p = 0.011$) **(Level of evidence 1++).**

In a subgroup analysis of EFFORT, patients with aging-related vulnerability receiving individualized early nutritional support compared with routine hospital food showed a >50% reduction in the risk of 30-day mortality (OR 0.48 95% CI 0.31 to 0.76; $p = 0.002$) [106]. In patients with chronic heart failure included in the EFFORT trial, Hersberger et al., 2021, reported that mortality over 30 days was 66% lower in the IG (OR 0.44 95% CI 0.26 to 0.75; $p = 0.002$) [107].

The above mentioned prospective RCT from Hegerová et al. [33] aimed to determine whether early nutritional therapy and exercise would influence the development of sarcopenia and impaired self-sufficiency during acute illness. Patients randomized to the CG received standard treatment, while in the IG ONS (600 kcal, 20 g/day protein) was added to the standard diet from day 1 of hospitalization (with a simultaneous intensive rehabilitation program). The amount of lean body mass in CG patients decreased during their hospital stay but did not change in the IG. Three months post-discharge, lean body mass was 3.5 kg lower in the CG but only 0.4 kg lower in the treated group. Lean body mass did not reach its original value even twelve months post-discharge in the CG, but it did in the IG. Regarding self-sufficiency (measured by independency in the activities of daily living through the BI, it diminished during the course of annual monitoring in both groups of patients, but the decline was sharper in the CG (**Level of evidence 1++**).

Zheng et al. [108] compared early EN (started on first day, $n = 75$) with "family managed nutrition" ($n = 71$) in a RCT of patients with acute stroke and dysphagia. The infection rate in the IG was significantly lower than that in the CG (33.3% vs. 52.1%, $p = 0.022$). Also, the IG showed a better NIHSS score than that of the CG after 21 days (12.04 ± 2.55) vs. 10.78 ± 2.69); $p = 0.008$). However, patients were admitted to the stroke unit in the IG and to the regular ward in the CG, which entails a high risk of bias (**Level of evidence 1-**).

Using a nationwide inpatient database with 432,620 eligible patients hospitalized for acute heart failure after propensity score matching, Kaneko et al. showed that delayed initiation of feeding (later than two days after admission) was associated with higher in-hospital mortality (OR 1.32, 95% CI1.26 to 1.39), longer LOS and higher incidence of pneumonia and sepsis when compared to earlier initiation of feeding (**Level of evidence 2-**) [109].

Two studies addressed budget impact analysis, performed using previously published outcomes data. Buitrago et al. in a secondary analysis applied to a Colombian population, found that average total costs over 60 days were 3770 $ for patients with delayed nutrition therapy vs. 2419 $ for patients with early nutrition therapy (started within 24–48 h of hospital admission) – a savings of 1351 $ (35.8% decrease) per nutrition-treated patient (**Level of evidence 2++**) [110]. A similar budget-impact analysis, applied to a Mexican population, reported average total healthcare costs over 30-days 3527 $ for patients with early nutrition therapy vs. 6032 $ for patients with standard nutrition therapy – a savings of 2505 $ per early nutrition-treated patient (41.5% lower). Cost differences between the groups were 2336 $ vs. 3065 $ for hospital-associated costs (23.8% lower), 262 $ vs. 780 $ for 30-day readmissions (66.4% lower) and 1348 $ for malnutrition-associated infections (**Level of evidence 2++**) [111].

Question 9. Does the continued use of nutritional support after discharge compared to nutritional support during inpatient stay alone affect the outcome of polymorbid patients?

For the present question, only interventions initiated in the hospital (and continued after discharge) were considered for inclusion. In case of doubt, authors were contacted to confirm this information.

3.20. Recommendation 20

In malnourished polymorbid medical inpatients or those at risk of malnutrition, nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients are commonly malnourished and frequently nutritional status does not improve but instead deteriorates during their hospital stay. As a result, many patients leave the hospital malnourished, or more malnourished, which increases the risk for functional decline, loss of independence and greater morbidity. Poor nutritional status is acknowledged to contribute to the recently described post hospital syndrome that represents a 30-day "generalized transient vulnerability following hospital discharge" leading to higher morbidity and an increased rate of unplanned readmissions [112]. Therefore, ensuring adequate nutritional intake during the transition from hospital to home is an important goal in malnourished patients. Systematic reviews found evidence for improved body weight and nutritional status in older patients after discharge either with individualized nutritional support [113] or intervention with ONS [114]. A recent meta-analysis also demonstrated that caloric intake but also protein intake was significantly higher in patients receiving nutritional support after hospital discharge (**Level of evidence: 1++**) [115]. Very few studies have, however, directly compared nutritional intervention in and after hospital discharge vs. nutritional support in hospital alone.

One study by Feldblum et al. which directly compared 6-month individualized nutritional support from a dietitian in hospital followed by three home visits after discharge [group 1, n = 66 (IG)] to either a single consultation with the dietitian in hospital or standard care [group 2 and 3, n = 102 (CG)], showed that continued nutritional support in malnourished patients aged ≥65 years resulted in a significantly higher change in mean MNA score, compared to the combined group 2 and 3 (3.01 ± 2.65 in the IG vs. 1.81 ± 2.97 in the CG, p = 0.004) [116] **(Level of evidence 1-)**. Similarly, in a prospective RCT of 80 patients aged 75 years or more admitted for acute disease and at risk for malnutrition, a 60-day intervention with ONS which started in hospital and was continued at home or in the nursing home resulted in maintained body weight and improved MNA scores (3.01 ± 2.65 vs. 1.81 ± 2.97), p = 0.004), whereas CG patients continued to lose weight [117] **(Level of Evidence 1++).**

Similar results were obtained in other RCTs. In a RCT of malnourished hospital inpatients (n = 47 in the IG and n = 46 in the CG) by Casals et al., the intervention resulted in increased body weight (4.750 ± 5.12 kg in the IG vs. −0.903 ± 6.12) kg in the CG, p < 0.001) and improved the MUST score (−2.457 ± 1.39 in the IG vs. −1.170 ± 1.67) in the CG, p < 0.001) after six months of continued nutritional counseling by case manager nurses (frequency of visits depending on severity of malnutrition, either every month or every second month) **(Level of Evidence 1-)** [118] and similarly, in a RCT of malnourished patients (according to the MNA-SF) aged 85 ± 6 years, individualized nutritional support for four months after discharge maintained body weight in the intention-to-treat analysis (difference in mean weight from baseline to 4-month follow-up was 0.6 kg in the IG vs. −1.5 kg in the CG, p < 0.001), although a high dropout rate was reported **(Level of Evidence 1+)** [119]. A sub-analysis of the NOURISH study showed an increase in nutrient intake in IG patients without decrease in dietary intake **(Level of Evidence 1-)** [98].

3.21. Recommendation 21

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and QoL.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

Improving functional status is one of the most important goals of nutritional therapy after discharge to prevent prolonged recovery, unplanned readmissions or loss of autonomy. Functional status can be assessed by objective measures such as HGS or walking speed, or by subjective measures, for example through the use of questionnaires on mobility and physical ability. QoL is a multidimensional construct to evaluate the success of treatments which has been increasingly used in RCTs of nutritional interventions. Due to the many influencing factors on health-related QoL, sufficient sample sizes are needed and effects of nutritional therapy on QoL might depend on the subjects' age, the underlying disease or the duration of nutritional therapy.

In one RCT conducted in malnourished adults aged ≥60 years admitted to an acute hospital for medical or surgical conditions, 3-month nutritional intervention (with energy and protein rich diets, ONS and calcium + vitamin D supplements, providing 600 kcal/day and 24 g protein/day as well as 400 IU vitamin D3 and 500 mg calcium) resulted in a reduction in the number of falls (10% vs. 24%, p = 0.02) [120] **(Level of Evidence 1++)**, a significant improvement in self-reported functional limitations (mean difference −0.72, 95% CI -1.15 to −0.28) [121], and was neutral in financial cost [122] **(Level of Evidence 1++).** On the other hand, increase in QoL did not differ between IG and CG receiving standard care [122] **(Level of Evidence 1++).** In the study by Persson et al., which included older patients at risk of malnutrition (85 ± 6 years), treatment with complete or incomplete liquid supplements (providing an average intake of 60 kcals and 11.25 g protein per day) and dietary advice for four months resulted in an improvement of Katz's activities of daily living index (p < 0.001; p = 0.05 between groups), but not in QoL assessed by the SF-36 [119] **(Level of Evidence 1+).** On the other hand, Casals et al. reported significantly improved QoL scores (assessed by SF-12, with a difference between IG and CG of 13.72, p < 0.001) after six months of individualized nutritional support [118].

In younger malnourished patients (50.6 ± 16.1 years) with benign gastrointestinal or liver disease who received ONS during their hospital stay and for three months post discharge, QoL assessed by the 36-Item Short Form Health Survey questionnaire was significantly improved in the IG patients (n = 60) compared to the CG patients (n = 54) (mean improvement at three months was 0.128, 95% CI 0.095 to 0.161 in the IG vs. 0.067, 95% CI 0.031 to 0.103 in the CG) [123] **(Level of Evidence 1+).** HGS and peak expiratory flow increased after three months only in the intervention patients (grip strength improved from 26.1 ± 11.3 to 31.5 ± 10.1 kg, p < 0.0001; and peak flow from 329.2 ± 124.0 to 388.9 ± 108.4 l/min, p = 0.004) [124] **(Level of Evidence 1+).** HGS was also significantly improved in the IG of malnourished patients after three months of ONS (twice a day (one drink providing 350 kcal, 20 g protein, 1.5 g calcium-βHMB), 160 IU vitamin D and other essential micronutrients)) in the NOURISH study **(Level of Evidence 1++)** [39].

A study which used multimodal nutritional approach (dietary counselling with a nutrition plan, telephone follow ups and free samples) in older malnourished patients showed a significant improvement in the 30 s chair rise test in the IG (7.2 ± 4.3 vs. 5.3 ± 4.1), p = 0.010). The improvements in physical function were significantly higher in the IG (Δ 4.2 ± 4.4 vs. Δ 2.2 ± 2.5), p = 0.008) but clinically relevant in both groups. Regarding QoL, the Q-5D-3L VAS-score was higher in IG at the end of the study compared to the CG (IG: 61.6 ± 16.2 vs. CG: 53.3 ± 19.3, p = 0.011) with a significantly higher increase in the IG (Δ 14.3 ± 15.5 vs. Δ 5.6 ± 17.2, p = 0.002). However, the calculated Q-5D-3L scores which reflect the overall multidimensional aspect of QoL did not differ between groups **(Level of Evidence 1+)** [125].

3.22. Recommendation 22

In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention shall be considered to lower mortality.

Grade of recommendation A – Strong consensus 96% agreement.

Commentary

The effect of nutritional intervention with ONS on mortality has not been frequently studied in sufficiently sized patient cohorts. One of the largest RCTs to date (NOURISH study; n = 652 patients aged 65 years or more with medical conditions) on in- and post hospital (=continued) nutritional support reported lower 90-day mortality in the IG receiving ONS twice a day (one drink providing 350 kcal, 20 g protein, 1.5 g calcium-βHMB), 160 IU vitamin D and other essential micronutrients) for three months compared to the CG patients who received a placebo (4.8% in the IG vs. 9.7% in the CG, p = 0.018) [9] **(Level of evidence 1++)**. In the study by Feldblum et al., the IG patients (>65 years) who received individualized nutritional support from a dietitian during hospitalization and for six month after discharge (three home visits after discharge) exhibited a significantly lower mortality rate (3.8%) than the CG (vs. 11.6%, p = 0.03) at month 6 [116]. The PICNIC study of Bonilla-Palomas et al. initiated nutritional intervention in patients with heart failure at admission to hospital and continued for six months. The intervention consisted of counselling with diet optimization and ONS in case nutritional goals were not reached. At twelve months, the primary composite endpoint (all-cause mortality and readmission due to deterioration of heart failure) occurred in 27.1% of the IG compared to 60.7% of CG patients (HR 0.45, 95% CI 0.19–0.62, p = 0.0004). **(Level of evidence 1+)**. Both mortality (HR 0.37, 95% CI 0.19–0.72, p = 0.003) and readmission rates were lower in the IG patients (10.2 vs. 36.1%, p = 0.001) [126]. The benefits of the nutritional intervention persisted at 24 months, as the primary endpoint occurred more frequently in of the CG patients (73.8%) compared to in 47.5% of IG patients (HR 0.45, 95% CI 0.28–0.72; p = 0.001). Thirty-nine % of the IG had died compared to 59% of the CG (HR 0.53, 95% CI 0.31 to 0.89; p = 0.017) **(Level of evidence 1+)** [127]. These effects did not differ comparing patients with hypoalbuminemia and with normalbuminemia [128] **(Level of Evidence 1+)**.

Also, a recently published systematic review and meta-analysis [115] including a total of 2438 patients concluded that mortality was significantly lowered in patients with nutritional support which was continued after hospital discharge (OR 0.63, 95% CI 0.48 to 0.84, p = 0.001, I^2 = 1%; 13 trials). However, trial quality was deemed moderate, highlighting the need for further large-scale studies **(Level of evidence 1++)**. Another meta-analysis by the same author group including 29 studies on nutritional support in hospital as well as continued nutritional support after hospital discharge (n = 7) also showed a 30% reduction in mortality in patients from the IGs (OR 0.72 95% CI 0.57 to 0.91, p = 0.006) **(Level of evidence 1++)** [78].

Only one study studied the impact of nutritional support on long-term mortality (> one year). A secondary analysis of the three-month RCT by Neelemaat revealed no differences in mortality at year one and four between groups (**Level of evidence: 1+**) [129].

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation 22 is limited to the subgroup of polymorbid older patients. For further information regarding the nutritional care of older patients, please refer to the existing ESPEN guidelines on EN and PN for geriatric patients [75].

The present recommendations highlight the need for ongoing review or monitoring nutritional support against patient specific goals post discharge (to establish whether continuation of medical nutrition therapy is needed) and the need for good quality communication of medical nutrition therapy regimens (whether oral, EN or PN) and goals of treatment in discharge documentation.

3.23. Recommendation 23

In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention should be considered for more than two months in order to lower mortality/impact clinical course.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

The ideal duration of post discharge nutritional intervention varies in all likelihood according to patients' age, underlying disease, initial nutritional status, type of nutritional support and endpoint of interest. However, in most RCTs on intervention with ONS, the sip feeds were given for at least three months [9,120–124], whereas individualized nutritional support (which might include ONS where necessary) was usually carried out for longer periods (e.g. four months in the study by Persson et al. [119], or six months in the studies of Feldblum et al. [116], Casals et al. [118], Bonilla-Palomas et al. [126], and Yang et al. [130]. A longer duration of nutritional support might explain differences in clinical outcome. While readmission rates as an indicator of clinical course e.g. were not reduced after three months in one of the largest trials to date **(level of evidence: 1++)** [9] in geriatric patients (**level of evidence: 1+**) [131] or in older patients (**level of evidence: 1-**) [132], it was significantly reduced after six months of nutritional intervention in several trials (**level of evidence: 1-)** [116] (**level of evidence: 1+**) [130] (**level of evidence: 1++**) [126] but not all (**level of evidence: 1+**) [125]. A recent meta-analysis also showed that interventions which lasted >60 days had a stronger effect on mortality (OR 0.53 95% CI 0.38 to 0.75) than trials with shorter durations of the intervention (OR 0.85 95% CI 0.64 to 1.13, p for subgroup difference: 0.04.) Among the predictors for the success of nutritional support were high protein supplementation (OR 0.57 vs. 0.93, I^2 = 86.3%, p for heterogeneity = 0.007) and long-term nutritional interventions (OR 0.53 vs. 0.85, I^2 = 76.2%, p for heterogeneity = 0.040). However, there was no effect on readmission rates in the meta-analysis, although only one study with data on readmission was included in which nutritional support was carried out for six months (**level of evidence: 1++**) [78].

In all likelihood, a longer duration of nutritional treatment is also necessary to improve QoL in older adults [133]. Neelemaat et al. argue that while they were able to show an effect on functional limitations in their older intervention patients after three

months, the length of nutritional support might not have been sufficient to show an effect on QoL (**level of evidence: 1+**) [122] which is similar to the results in the trial of Munk et al. (**level of evidence: 1+**) [125].

Question 10. Does the monitoring of physical functions, when it is possible, compared to monitoring of nutritional parameters (e.g. body weight, energy and protein intakes), improve other outcomes in polymorbid medical inpatients receiving nutritional support?

3.24. Recommendation 24

While nutritional and functional parameters should be monitored to assess responses to nutritional support, functional indices may be more appropriate in assessing other clinical outcomes (i.e., survival, QoL) in polymorbid medical inpatients and should be used for this purpose.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

Limited evidence exists to answer this clinical question precisely. Most trials assessing the impact of nutritional support in polymorbid inpatient used nutritional and functional status as outcome rather than as monitoring tools of the efficacy of nutrition intervention in improving other outcomes.

A secondary analysis from the recent large EFFORT trial (described before) supports the use of functional parameters to monitor nutritional support but also to guide the initiation of it. Kaegi-Braun et al. illustrates in 1809 polymorbid medical inpatients at nutritional risk that individualized nutritional support was most effective in reducing mortality in patients with low HGS (adjusted OR 0.29, 95% CI, 0.10 to 0.82 in patients in the ≤10th percentile compared with OR 0.98, 95% CI, 0.66 to 1.48 in patients in the >10th percentile; P for interaction = 0.026). This result demonstrates the value of a low HGS in predicting response to nutritional support, which may be a useful tool in clinical practice. Furthermore, an incremental decrease of HGS by 10 kg resulted in more than doubling 30-d mortality in females and a 50% increase in 30-d mortality in males, reflecting the prognostic potential of HGS [134] (**Level of evidence 1++**).

In a cohort study from 2021 by Ballesteros-Pomar et al., 200 polymorbid medical inpatients were included. They determined the impact of low muscle mass and strength on clinical outcome and found that a higher HGS, but not muscle mass, was related to better QoL (total QoL: Beta = −0.323, p = 0.001 and QoL visual analogue scale (VAS): Beta = 0.360, p < 0.001), less readmissions (OR = 0.95, p = 0.026) and lower mortality (OR = 0.85, p = 0.014) after adjusting for age, sex, and comorbidity [135] (**Level of evidence 2++**). However, another prospective observational study failed to show a significant association between HGS and 100-day mortality [136] (**Level of evidence 2-**).

In a study from 1995, Mendehall et al. [137] studied 271 polymorbid medical inpatients with severe alcoholic hepatitis and randomly assigned to oxandrolone therapy plus a high-energy, high-protein supplement (active treatment) or placebo plus a low-energy, low protein supplement (standard treatment). During treatment, energy and protein intake increased significantly in the active treatment group vs. standard treatment (2312 kcal vs. 1495 kcal (p < 0.001) and 89 g vs. 57 g protein (p < 0.001), respectively), leading to a significantly better mid-arm muscle area (change 4.5 vs. 0.3, p = 0.02), creatinine-height index (change 18.4 vs. 2.6, p = 0.03) and % ideal body weight (change 8.1 vs. 2.3, p = 0.04). Interestingly, active treatment did not improve HGS better than standard treatment. However, when assessing the impact of nutrition intervention on 6-month mortality, Mendehall et al. reported that creatinine-height index, total lymphocyte count and HGS are the stronger predictors. This suggests that although nutrition therapy improves nutritional status and outcome (i.e., they are tools to assess the response to therapy), functional parameters are more robust prognosticators of outcome **(Level of evidence: 1-).**

Norman et al. [124] studied 80 malnourished polymorbid patients with gastrointestinal benign disease. After discharge from the hospital, patients were randomized into two groups: one group received for three months dietary counseling plus a standard ONS (IG) whereas the other group received only dietary counseling (CG group). At baseline, no difference was observed in nutritional (i.e., SGA, body composition) and functional parameters (i.e., peak flow, HGS) as well as in QoL (SF-36) between the two groups. At the end of the study, both body weight and body cell mass improved significantly in both groups. However, HGS (change from 26.1 to 31.5 kg, p < 0.0001) and peak flow (change from 329.2 to 388.9 l/min, p = 0.004) improved only in the IG. Also, all SF-36 subscales (n = 8) significantly improved in IG patients, whereas only three (physical functioning, bodily pain and vitality) improved in CG patients. Of interest, the change in HGS correlated with the change in two SF-36 physical scales (i.e., physical functioning and role physical). By applying the reasoning used for the trial by Mendehall et al., it appears that Norman et al. confirm that functional parameters may be superior to nutritional parameters in assessing other clinical outcomes in polymorbid medical inpatients receiving nutritional support **(Level of evidence: 1-).** Supporting our interpretation of the available literature, Koretz et al. [138] analyzed 99 RCTs of nutritional support vs. no nutritional support which reported at least one clinical outcome and at least one nutritional outcome. The authors' assumption was that if changes in nutritional markers predict clinical outcome, changes in both outcomes should go in the same direction. Therefore, the 99 clinical trials were assessed for concordance. The results showed that the rates of concordance were quite low and never >75%. The discordance was usually a result of the nutritional outcome being stronger than the clinical outcome. Koretz et al. concluded that based on their analysis, changes in nutritional markers do not predict clinical outcomes. More recently, Jeejeebhoy et al. [139] prospectively studied 733 patients with complete nutritional intervention data to assess which nutrition indicator better predicts LOS and readmission within 30 days after discharge. After having controlled for age, sex, and diagnosis, only SGA C and reduced food intake during the first week of hospitalization resulted as independent predictors for LOS. SGA C and HGS but not food intake were independent predictors of 30-day readmission. This study appears to suggest that nutritional parameters may serve well as monitoring tools to predict other clinical outcomes.

Question 11. Does meeting more than 75% of energy and/or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid medical inpatients receiving nutritional support?

3.25. Recommendation 25

In polymorbid medical inpatients with reduced food intake and hampered nutritional status, at least 75% of calculated energy and protein requirements shall be achieved in order to reduce the risk of adverse outcomes and mortality.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

In polymorbid medical inpatients reduced food intake is more the rule than the exception [140] and is often an important part of

the complex symptomatology that forces the patient to the hospital. Reduced food intake has several commonly occurring determinants, including anorexia, dysphagia and oral and dental problems. There are numerous studies indicating that reduced food intake is associated with increased mortality and with complications like infections in medical patients. For example, reports from the large database of the "NutritionDay" initiative demonstrate that reduced food intake during the day of food intake assessment is related to increased in-hospital mortality [141,142]. Likewise, a study on approximately 1100 recently hospital-admitted patients with mixed diagnoses showed that 16% had a food intake below 70% of calculated energy requirement [143]. This energy intake was cross-sectionally associated with an increased risk of infections; adjusted odds ratio being 2.26, 95% CI 1.24 to 4.11.

The EFFORT trial has demonstrated that reaching at least 75% of estimated energy and protein goals versus lower achievements of goals led to significant lower risk of adverse events and mortality (adjusted OR 0.79, 95% CI 0.64 to 0.97 and 0.65, 95% CI 0.47 to 0.91 [8] (**Level of evidence 1++**). Whether the impact would be more pronounced if the IG had achieved 100% of the calculated targets cannot be answered by the data. Achieving 100% of the targets should be strived for, but is usually not realistic when patients are hospitalized and have either an exacerbation of one of their conditions or a current complication. Supporting this finding in a meta-analysis from 2019, Gomes et al. [35] stratified trials by adherence to nutrition protocol and found that in trials with high adherence there was a more pronounced survival benefit (OR 0.67, 95% CI 0.54 to 0.84) compared to trials with low adherence (OR 0.88, 95% CI 0.44 to 1.76). There was also a significant higher energy intake and weight change in the subgroup of high adherence (**Level of evidence 1++).**

In a good quality prospective observational study [144] (**Level of evidence 2++),** of close to 500 polymorbid patients admitted either to a medical service or to a surgical service with mixed diagnoses, 21% had an average nutrient intake of less than 50% of calculated energy needs. Only patients with a hospital stay of more than four days were included in this study. Although baseline characteristics according to demography and diseases were quite similar, patients with reduced food intake had a higher in-hospital mortality as well as 90-day mortality with relative risks of 8.0, 95% CI 2.8 to 22.6 and 2.9, 95% CI 1.4 to 6.1, respectively.

Similar results were observed in a supportive study conducted in the critically ill population [145]. 28-day mortality was registered in a sequential series of 886 mechanically ventilated critically ill patients with both medical and surgical diagnoses, where nutrition was provided either by the enteral (73%) or enteral combined with parenteral routes (26%). The energy target was guided by IC and protein target calculated as 1.2–1.5 g/kg body weight/day. The group of patients who reached their target for both energy and protein needs had a 28-day mortality that was half that of those patients who did not achieve their target. A non-ICU trial Li et al. found nutritional intake to be higher in patients with LOS of less than twelve days compared to patients with higher LOS [21] (**Level of evidence 2-**).

However, a small sample size (n = 40) pilot RCT could not find a difference in readmissions within 30 days between the IG that reached 75% of their nutritional goals and the CG that did not [146] (**Level of evidence 1-**).

A further question is what the optimal amount of nutrition is, or what is the least dose of nutrition needed to achieve potential beneficial effects. Within nutrition support treatment plan the aim is to archive 100% of calculated needs but it has to be taken into account that an acute disease triggers inflammation and several catabolic processes in the body, which will hamper the body's capability to handle energy and protein for growth. Therefore, there is now growing evidence that 75% of calculated needs could be a goal to achieve for energy and protein intake during the hospital stay and when the disease is still in an acute catabolic phase. But also within these populations there are differences in treatment response mainly explained by severity of acute phase [147]. Consequently the question is raising if there is a need for more precise nutritional goals or nutritional therapy.

3.26. Recommendation 26

In polymorbid medical inpatients who are malnourished or at high risk of malnutrition, able to safely receive nutrition orally, and cannot tolerate or wish not to receive ONS, food fortification can be considered an effective way in order to reach relevant energy and protein targets and in improving nutritional intake.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

There is now growing evidence that reaching 75% of energy and protein goals has a profound impact on clinical outcome as described before. To reach these goals different approaches can be used. A Danish RCT [148] tested the hypothesis that protein fortification of a novel energy dense menu supplementary to the standard hospital food service could increase the food based nutrition intake of energy and protein beyond 75% of calculated requirements **(Level of evidence 1+).** The target population was newly-admitted polymorbid medical inpatients classified as at nutritional risk by NRS 2002. The RCT was well-conducted but too small for providing any evidence on clinical outcome measures. Altogether 81 patients fulfilled the study protocol. The novel menu consisted of protein fortified small energy dense dishes that could be ordered by telephone from the hospital kitchen by the patients from 7 h to 22 h. This intervention significantly improved the energy and protein intakes and also the number of patients that reached the protein target (calculated as 18% of energy intake), i.e. 66% reached the target compared to 30% in the CG. HGS and LOS were also reported but there were no differences to be observed, as expected when the study was not powered for such end-points.

Another supportive study is a Dutch RCT [77], which used protein-enriched familiar foods and drinks (intervention products) to improve protein intake in older hospitalized polymorbid patients. More patients in the IG than in the CG (standard energy and protein rich hospital menu) reached a protein intake of 1.2 g/kg/day (79.1% vs. 47.5%, respectively). Both studies demonstrate that there are effective alternative besides ONS to improve energy and protein intake in hospitalized polymorbid patients.

Another important aspect is that provision of nutritional support via ONS is often discontinued or not well tolerated by hospitalized patients. Taste and texture preferences, limited taste variety and the fact that ONS are not always perceived as food, especially by older adults, often limit the patients' compliance [149,150]. According to a meta-analysis by Mills et al., provision of energy or protein in the form of fortified foods or supplements in food items in a population of patients in acute and rehabilitation state resulted in energy intake increased by 250–450 kcal/day and protein intake increased by 12–16 g/day. According to these results, fortification and supplementation of common food items could be considered a cost-effective, well tolerated and effective way of improving nutrient intake in older inpatients [151]. In another systematic review and meta-analysis on the effect of food fortification in older adults by Morilla-Herrera et al., positive and cost-effective results were reported in terms of dietary energy and protein intake compared to the usual care, but the need of higher quality studies was stressed out [152]. Moreover, studies on the effect on food fortification vs. ONS in hospitalized patients could also be of interest.

Question 12. Do organizational changes in nutritional support (e.g. intervention of a steering committee, implementation of protected mealtimes, different budget allocation) versus no changes improve outcomes of polymorbid medical inpatients?

3.27. Recommendation 27

Organizational changes in nutrition support provision like enriched menus should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition to improve intake and nutritional outcome.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

The organization of nutritional support in hospitals requires a multi-disciplinary approach involving finance, catering, nursing and therapy services. Some general studies have suggested that changes to the organization of nutritional support for in-patients may improve outcomes. These include the use of nutritional healthcare assistants [153], targeted education for dietitians and the MDT to improve early use of ONS [154], food fortification [155], introduction of a nutrition screening tool [156] and technological innovations used at an organizational level to facilitate timely referral to the Nutrition Support Team (NST) [157].

Despite these interesting studies in non-polymorbid patients, a systematic review of non-randomized studies showed that improvements are not consistently demonstrated [158]. Therefore, it is important to consider the specific impact of organizational changes on polymorbid medical inpatients. A single-blinded RCT [148] demonstrated how the use of a protein fortified menu was effective in increasing the protein intake of patients. The IG was able to choose from a protein enriched menu in addition to the standard hospital menu. The CG received the standard hospital menu. There was no significant difference in energy intake, LOS or HGS between groups. However, mean protein intake was significantly increased in the IG; with 27/41 compared to 12/40 in the CG meeting ≥75% protein requirements ($p = 0.001$). **(Level of Evidence 1+).**

A pilot, controlled trial in older patients ($n = 122$) on a subacute ward compared a modified hospital menu, including higher energy and protein choices, to the standard hospital menu [159]. Patients were allocated to IG or CG depending on their room, with the rooms on one side of the ward receiving the intervention and the other side receiving the control. Measures were taken at baseline and after 14 days. Data were missing for 41.1% of patients on day 14. In those with complete data, there was no difference in patients' weight, HGS, functional independence measure or LOS. However, energy (1725 kcal/day vs. 1863 kcal/day, $p = 0.21$) and protein (76 g/day vs. 80 g/day, $p = 0.59$) intake were higher in the IG. This increase was statistically significant when adjusted for weight ($p = 0.03$ for protein, $p = 0.003$ for energy intake) **(Level of evidence 1-)**.

A further, prospective controlled trial [160] involving 298 polymorbid geriatric inpatients, demonstrated the use of an early multi-disciplinary intervention protocol including activities such as nutrition and dysphagia screening, patient positioning and individualizing time of meals. This was compared to standard care in the management of older patients at high risk of protein energy malnutrition across two sites. A significant weight gain (mean + 0.9 kg) was observed in the IG, whereas a weight loss (mean −0.8 kg) was observed in the CG, during admission. Mean LOS was approximately 32 days in both groups. In addition, the IG developed fewer hospital acquired infections (33/140 compared to 58/158, $p = 0.01$). There was no statistically significant difference in the development of pressure ulcers or LOS **(Level of Evidence 2+).**

3.28. Recommendation 28

Organizational changes, particularly the establishment of a NST and the use of multidisciplinary nutrition protocols, should be implemented in polymorbid medical inpatients at risk for malnutrition.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

Several observational studies have considered the effect of introducing broad organizational changes. A cohort study involving 207 adult acute medical patients reported the impact of multiple nutrition improvement initiatives on a one-day record of intake of estimated energy and protein requirements (>75% of requirements) [161]. Initiatives included a magnetic traffic light symbol above the patients' bed to identify nutritional risk, tailored education for nursing, medical and food service staff, and menu changes to include a full and hot breakfast option. Breakfast service was moved to an earlier time to avoid interruptions from ward rounds and clinical interventions. The number of patients achieving adequate energy and protein intake increased significantly from pre-intervention to post-interventional. It is suggested that this increase in intake was primarily a consequence of introducing the hot breakfast option **(Level of Evidence 2+).**

Young et al., reported the implementation of nutrition improvement initiatives over a seven-year period on three medical wards [162]. The primary outcome was energy and protein intake observed on a single day between day three and seven of the patients' admission. Phased initiatives included the introduction of assisted mealtimes, an assistant in nursing to assist with nutrition administration/feeding assistance and additional education for nurses, dietitians and the wider MDT. Results showed a significant difference in energy intake between cohorts (cohort 1: 1212 kcal/day (SD 442), cohort 2: 1291 kcal/day (SD 538), cohort 3: 1431 kcal/day (SD 625), $p = 0.04$). Protein intake increased significantly in each successive cohort (+48 g/day (SD 19), +50 g/day (SD 21) and+57 g/day (SD 26) respectively, $p = 0.02$). These three studies suggest that a combination of organizational changes may be sustained over a period of time and culminate in improved dietary intake **(Level of Evidence 2+).**

In another mealtime assistant study, trained volunteers assisted patients for one year [163]. Volunteers received a half-day training, and provided mealtime assistance at weekday lunchtimes to patients who were identified to need help by a nurse. The authors reported their intervention to potentially release time for nursing staff but, however, found no positive effect on dietary intake **(Level of Evidence 1+)**.

In terms of artificial nutritional support, a cohort study [164] demonstrated the impact of an NST on the management of patients requiring, or referred for, PN. After a structured training program for nurses led by the NST, catheter-related sepsis rates decreased in PN patients from 71% pre-NST to 29% in their first year ($p = 0.05$). Additionally, 55 episodes of PN (41% of referrals) were avoided by appropriate NST assessment and rapid instigation of enteral feeding **(Level of Evidence 2+)**.

Where a controlled trial found no difference in the energy or protein intake of older female patients with the implementation of mealtime volunteers, volunteers were as effective as ward nursing staff in providing appropriate feeding assistance. This suggests that mealtime volunteers may be successfully implemented to release nursing staff to carry out other clinical tasks [161] **(Level of Evidence 1+).**

Thus, the evidence shows that organizational changes in nutritional support provision can improve energy and protein intake and reduce the risk of adverse outcomes in polymorbid medical

inpatients. The use of conceptual frameworks to implement changes has been successful in some studies [161,162].

Question 13. Does underlying disease have an impact on expected outcome from nutritional support?

3.29. Recommendation 29

The severity of acute-phase response should be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

There is growing evidence that type of underlying disease, severity of disease and extend of the acute-phase reaction have an impact on the effect of nutrition therapy [165]. Thereby, inflammation is a key factor with several important metabolic effects on a cellular level (e.g., increase in insulin resistance leading to an inhibition of nutrition entering cells) and on different organs such as the brain (e.g., causing disease-related anorexia and reduced food intake), the intestines and on muscle (e.g., causing catabolism and sarcopenia). Interestingly, recent data also suggest that inflammation modulates the response to nutritional treatment. A double-blind randomized trial of nutritional supplementation published [166] by Gariballa et al., in 2006, including 445 polymorbid patients, concluded that the acute-phase response was strongly associated with poor nutritional status and worse clinical outcomes, particularly in older patients (**Level of evidence: 1++**). There are also studies showing that patients with high inflammation do not show a positive response to nutritional interventions while patients with lower levels of inflammation did. A secondary analysis of the multicentre randomized-controlled EFFORT trial suggested that patients with CRP levels of ≥100 mg/l no longer responded to nutritional therapy, while patients with lower levels had a significant mortality benefit from nutritional support [147] (**Level of evidence: 1++**). A similar association was also found for cancer patients, with a significantly extenuated response to nutrition in patients with high inflammation [167]. These findings may also explain differences in results of nutritional trials, depending on the clinical setting with several nutritional studies in the ICU setting or in patients with advanced cancer not showing significant benefits form nutrition in regard to clinical outcomes [165,168]. Clearly, there is need for additional research to confirm the relationship between acute-phase response, expected outcome and response to nutritional support to understand the optimal timing and composition of nutritional therapy in an individual patient, based on the acuity of illness and the metabolic stress.

3.30. Recommendation 30

Underlying disease modifies the effect of nutritional therapy and should be considered when initiating nutritional support.

Grade of recommendation B – Strong consensus 92% agreement.

Commentary

There is strong evidence from large RCTs that polymorbid patients at risk for malnutrition benefit from nutritional support [36]. In a population-based cohort study of more than 110,000 patients, effect of nutritional support remained robust in subgroup analyses which stratified for main diagnoses and comorbidities, among others [169] (**Level of evidence: 2-**). However, among medical patients, the effect of nutritional support may also depend on underlying disease. Characterisation of the polymorbid patient may therefore help to provide optimal nutritional care. Still, understanding the interplay of different chronic and acute diseases is challenging and needs further research. Mudge et al. identified diagnosis of infection or cancer to be associated with inadequate energy intake in patients aged 65 years or older [170] (**Level of evidence: 2++**). A recent study by Bargetzi et al. found that kidney disease predicted response to nutritional treatment with lower estimated glomerular filtration rates [eGFR] showing stronger clinical benefit [89] (**Level of evidence: 1++**). Similarly, patients with chronic heart failure have shown strong benefit from nutritional support. A survival benefit in chronic heart failure patients receiving nutritional support was found in a Spanish trial by Bonilla-Palomas et al. with 120 patients [126] (**Level of evidence: 1++**) and in secondary analysis of 645 patients from a randomized trial by Hersberger et al. [107] (**Level of evidence: 1++**). Similar results were also found within the NOURISH study with a significant survival benefit associated with nutritional support [9] (**Level of evidence: 1++**). Other conditions which may increase the effects of nutritional support are cancer [171], COPD [39] among others. However it remains unclear how to implement these findings into clinical routine.

Question 14. Are there risks of polypharmacy and drug–nutrient interaction in polymorbid medical inpatients?

3.31. Recommendation 31

In polymorbid medical inpatients there is an important possibility of drug–drug or drug–nutrient interactions that needs to be taken into account, therefore, a pharmacist-assisted management plan for any interactions should be established.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients will often require the prescription of multiple medicines in order to manage their comorbidities. Whilst the use of multiple medicines is often essential, it can present a number of risks that include potential 'drug–drug' and/or 'drug-nutrient' interactions. Indeed, as the number of medicines required increases so does the risk of these interactions as well as the risk of potential effects on nutritional status. For example, a systematic review of polypharmacy defined as ≥5 medicines in subjects ≥65 years of age was significantly associated with malnutrition [172], and polypharmacy when defined as >10 medicines was associated with an increased risk of malnutrition after three years in those >75 years [173]. Polypharmacy has been associated with sarcopenia [174], which could result in insufficiency of some electrolytes or micronutrients [175]. A recent meta-analysis from 2023, which included 29 studies, demonstrated that sarcopenia is associated with a higher prevalence of polypharmacy (OR: 1.65 [1.23, 2.20], $p < 0.01$) and higher number of medications (mean difference: 1.39, 95% CI 0.59 to 2.19, $I^2 = 95\%$, $p < 0.01$) compared with individuals without sarcopenia [176]. Side effects of medicines affecting body systems are described by Yoshimura et al. [177]. Such adverse effects from medicines on body systems could affect the status of specific types of nutrients. Doses of medicines may need to be adjusted or other changes to the clinical management and monitoring of patients may be necessary, with examples including patients with comorbidities in addition to human immunodeficiency virus infection [178,179] or psoriasis [180]. It is, however, important that care is taken to not only consider interactions that may be more familiar. For example, many healthcare professionals are familiar with the physical binding of drugs such as tetracyclines to the divalent and trivalent cations found in milk or antacid preparations [181] or in many of the ONS and enteral formulas, which limits absorption from the gastrointestinal tract.

Fewer are likely to be familiar with the potential for physical binding of ceftriaxone to calcium salts when each is given intravenously [182] or that hydration status, which is for example commonly impaired in acute medical admissions [183], can affect drug enrichment [184]. A holistic approach to assessment of hydration status of older people rather than the use of some individual tests may be necessary [185]. It is also important that care is taken to not only account for dietary intake but also oral fluid intake when considering potential drug–nutrient interactions. This is because whilst drugs such as simvastatin have no specific requirement to be taken with or without food it has the potential to be toxic when taken concurrently with grapefruit juice [186]. A description of pharmacokinetic interactions between food and drugs is available [187]. Advice on the complexities of all these potential interactions in polymorbid medical inpatients may be obtained from a pharmacist or a pharmacologist. We suggest that a review of medication is undertaken to identify unnecessary medications or medications that have side-effects which may compromise nutritional intake.

In summary, while some of the recommendations for screening, assessment and provision of nutritional support in polymorbid medical inpatients may not differ significantly from those recommendations applicable to single-disease patients, we have identified certain aspects of these patients' care that require particular attention, such as the identification of drug–drug or drug–nutrient interactions and the importance of continuing nutritional support after hospital discharge.

One of the strengths of this study was the conduct of the literature searches for all the clinical questions by a single author, which allowed the use of a systematic methodology to identify potentially relevant publications. This is particularly important for the present guidelines because, when compared to disease-specific guidelines, the methodology used for the identification of potentially relevant studies was more complex, as many of the published studies did not report data on the presence of multiple comorbidities or did not use typical key terms for this purpose. Additionally, there are no MeSH terms dedicated to multiple chronic conditions [3]. Consequently, we have not used search terms to define polymorbidity during the literature searches; instead we used different strategies to identify studies conducted in polymorbid populations, including the contact of authors to obtain further information on the presence of multiple comorbidities. In this context, we would encourage all authors of future trials to report data on polymorbidity.

Furthermore, due to the complex nature of the needs of polymorbid medical inpatients, we would encourage access to dietetic expertise to assess, manage and monitor nutritional status and nutritional intervention, whenever possible. Community-based approaches are also encouraged for the non-hospitalized polymorbid patients at nutritional risk, allowing for prevention (of the deterioration of their nutritional status) and an early intervention.

Question 15. Are there nutritional biomarkers that predict the response to nutritional treatment?

3.32. Recommendation 32

Specific nutritional biomarkers can be used to predict the response to nutritional support in polymorbid medical inpatients and therefore may help to personalize nutritional treatments.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

Finding specific nutritional biomarkers to predict the response to nutritional treatment is an emerging field in clinical research. Several studies and secondary analyses of trials within the polymorbid medical inpatient population have found that markers of inflammation, muscle strength, kidney function among others may help to further individualize treatment [165]. This concept of "personalized" nutrition is based on the observation that not all patients show the same response to nutritional interventions. For example, it has been known for long that patients with cachexia may show less response compared to patients with less severe stages or phenotypes of malnutrition [165,188]. There are several other factors and conditions which may predict whether or not a patient benefits from nutritional therapy including illness-specific factors (comorbidities, inflammation, acute vs. chronic course) or patient-specific factors (age, gender and genetic vulnerability).

While there are several biomarkers that have been proposed historically based on pathophysiological considerations (e.g., transthyretin, albumin, retinal-binding globulin) [189], only few have really been subject to rigorous scientific evaluation. Markers of inflammation (i.e. C-reactive protein [CRP]) have been shown to correlate with disease-related anorexia, reduced food intake and muscle catabolism, and at the same predict lack of response to nutritional treatment [147,190,191]. In a secondary analysis of EFFORT, unlike patients with lower CRP concentrations ($\leq$100 mg/L), patients with high inflammation (defined as CRP level >100 mg/L) did not respond to nutritional support [147] **(Level of evidence 1++).** Similarly, markers of chronic kidney dysfunction (i.e., creatinine) are associated with renal cachexia and weight loss, but patients with reduced kidney function show a particularly stronger response to nutritional treatment [8] **(Level of evidence 1++).** Albumin and prealbumin levels also have a strong prognostic value, but little correlation with nutritional response [192,193] **(both Level of evidence 1++).**There are several studies looking at biomarkers of muscle strength and/or function with some suggesting that low muscle strength measured by HGS is a predictor for response [134] **(Level of evidence 1++)** while others found sarcopenia to be a predictor of non-response in mixed populations [165,188].

There are also efforts to find certain metabolites as biomarkers to predict treatment response. In a secondary analysis of the EFFORT trial from 2022, Struja et al. used an untargeted proteomics approach to find predictive and prognostic metabolites. They concluded, due to high heterogeneity and small sample size, that so far the metabolites had only little prognostic and therapeutic potential for phenotyping the risk of malnutrition and response to nutritional therapy [194] **(Level of evidence 1++).** Until now there are no studies using a targeted proteomics approach.

Currently, no specific blood biomarkers of treatment response are used in routine clinical care apart from physiological nutritional markers such as weight and weight-loss, appetite among others although data from large RCTs suggest that their use might be advantageous. Thus, there is need for additional validation of results before wide-spread use in clinical routine.

4. Conclusions

This guideline provides 32 practical and non-disease specific recommendations to guide clinicians treating polymorbid patients. Recent high-quality RCTS have provided increasing evidence that nutritional support can reduce morbidity and other complications, which is reflected by several A and B recommendations. The practical recommendations cover the most relevant aspects of nutrition support (screening, assessment, nutritional requirements, monitoring and procedure of intervention) and provide a glimpse into the future, where individualization of nutritional therapy will become increasingly important. Nevertheless this work also allowed gaps in the literature (areas with little or no evidence) to be identified which require further research.

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Disclaimer

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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 with legitimate interest upon request to the ESPEN executive.

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Appendix A. Supplementary data

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