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ESPEN guidelines on nutritional support for polymorbid internal medicine patients

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SUMMARY

Background & aims: Polymorbidity (also known as multimorbidity) – defined as the co-occurrence of at least two chronic health conditions – is highly prevalent, particularly in the hospitalized population. Nonetheless, clinical guidelines largely address individual diseases and rarely account for polymorbidity. The aim of this project was to develop guidelines on nutritional support for polymorbid patients hospitalized in medical wards.

Methods: The methodology used for the development of the current project follows the standard operating procedures for ESPEN guidelines. It started with an initial meeting of the Working Group in January 2015, where twelve key clinical questions were developed that encompassed different aspects of nutritional support: indication, route of feeding, energy and protein requirements, micronutrient requirements, disease-specific nutrients, timing, monitoring and procedure of intervention. Systematic literature searches were conducted in three different databases (Medline, Embase and the Cochrane Library), as well as in secondary sources (e.g. published guidelines), until April 2016. Retrieved abstracts were screened to identify relevant studies that were used to develop recommendations, which were followed by submission to Delphi voting rounds.

Results: From a total of 4532 retrieved abstracts, 38 relevant studies were analyzed and used to generate a guideline draft that proposed 22 recommendations and four statements. The results of the first online voting showed a strong consensus (agreement of >90%) in 68% of recommendations and 75% of statements, and consensus (agreement of >75–90%) in 32% of recommendations and 25% of statements.

Abbreviations: BI, Barthel Index; βHMB, β-hydroxy β-methylbutyrate; CG, Control Group; DRM, disease-related malnutrition; EN, enteral nutrition; GEB, Guidelines Editorial Board; IC, indirect calorimetry; IG, Intervention Group; LOS, length of hospital stay; MNA(-sf), Mini Nutritional Assessment (short form); NRS 2002, Nutritional Risk Score 2002; 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; SGA, Subjective Global Assessment; SIGN, Scottish Intercollegiate Guidelines Network; TEE, total energy expenditure; WG, Working Group.

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At the final consensus conference, a consensus greater than 89% was reached for all of the recommendations.
Conclusions: Despite the methodological difficulties in creating non-disease specific guidelines, the evidence behind several important aspects of nutritional support for polymorbid medical inpatients was reviewed and summarized into practical clinical recommendations. Use of these guidelines offer an evidence-based nutritional approach to the polymorbid medical inpatient and may improve their outcomes.

1. Introduction

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 [1–3] and discussions within the guideline Working Group (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.

Topic	Clinical question and recommendation(s)/statement(s)
Indication	**1. Does nutritional support based on screening and/or assessment versus no screening and/or assessment improve outcomes in polymorbid inpatients?** *Recommendation 1.1* *In polymorbid medical inpatients, a quick and simple nutritional screening method using different validated tools should be applied to identify malnutrition risk. In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to consent an early adequate nutritional therapy and to define quality outcome measures of success.* *(Grade of recommendation B) – strong consensus (100% agreement)*
Route of feeding	**2. In polymorbid inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements (ONS), with or without nutritional counseling, versus no ONS, improve outcomes?** *Recommendation 2.1* *In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely reach their nutritional requirements orally, ONS high in energy and protein shall be considered to improve their nutritional status and quality of life.* *(Grade of recommendation A) – strong consensus (95% agreement)* *Recommendation 2.2* *In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutrient-specific ONS should be administered, when they may maintain muscle mass, reduce mortality or improve quality of life.* *(Grade of recommendation B) – consensus (89% agreement)* *Recommendation 2.3* *In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely reach their nutritional requirements orally, ONS should be considered as a cost-effective way of intervention towards improved outcomes.* *(Grade of recommendation B) – strong consensus (95% agreement)* **3. In patients where nutritional requirements cannot be met orally, does the use of enteral nutrition (EN) compared to parenteral nutrition (PN) (total or supplemental) result in improved outcomes in polymorbid inpatients?** *Recommendation 3.1* *In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN can be administered. In these cases, the use of EN may be superior to PN because of a lower risk of infectious and non-infectious complications.* *(Grade of recommendation 0) – strong consensus (100% agreement)*
Energy requirements	**4. Does the estimation of energy requirements with a prediction equation versus a weight-based formula improve outcomes of polymorbid inpatients requiring nutritional support?** *Recommendation 4.1* *Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula.* *(Grade of recommendation 0) – strong consensus (96% agreement)* *Recommendation 4.2* *In the absence of IC, total energy expenditure (TEE) for polymorbid older patients (aged >65 years) can be estimated using the formula 27 kcal/kg actual body weight. Resting energy expenditure (REE) can be estimated using the formula 18–20 kcal/kg body weight with the addition of activity or stress factors to estimate TEE.* *(Grade of recommendation 0) – strong consensus (95% agreement)* *Recommendation 4.3.a* *In the absence of IC, REE for severely underweight patients can be estimated using the formula 30 kcal/kg body weight.* *(Grade of recommendation 0) – consensus (89% agreement)* *Recommendation 4.3.b*

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(*continued*)

Topic	Clinical question and recommendation(s)/statement(s)
	This target of 30 kcal/kg 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)*
Protein requirements	**5. Do protein targets higher than 1.0 g/kg BW/day versus a lower target improve outcomes in polymorbid inpatients requiring nutritional support?** *Recommendation 5.1* *Polymorbid medical inpatients requiring nutritional support shall receive a minimum of 1.0 g of protein/kg of body weight per day in order to prevent body weight loss, reduce the risk of complications and hospital readmission and improve functional outcome. (Grade of recommendation A) – strong consensus (95% agreement)*
Micronutrients requirements	**6. In patients exclusively fed orally, does the supplementation of micronutrients (vitamins and trace elements) compared to no supplements improve outcomes in polymorbid inpatients?** *Recommendation 6.1* *In polymorbid medical inpatients exclusively fed orally adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured. (Grade of recommendation GPP) – strong consensus (100% agreement)* *Recommendation 6.2* *Polymorbid medical inpatients exclusively fed orally with documented or suspected micronutrient deficiencies should be repleted.* *(Grade of recommendation GPP) – strong consensus (93% agreement)*
Disease-specific nutrients	**7. Does disease-specific nutritional supplementation (e.g. fibre, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard formulations improve outcomes in polymorbid inpatients?** *Recommendation 7.1* *In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and β-hydroxy β-methylbutyrate (ßHMB) can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.* *(Grade of recommendation 0) – consensus (90 % agreement)* *Recommendation 7.2* *In polymorbid medical older inpatients requiring enteral nutrition, formulas enriched in a mixture of soluble and insoluble fibers can be used to improve bowel function.* *(Grade of recommendation 0) – strong consensus (95% agreement)*
Timing	**8. Does early nutritional support (i.e. provided less than 48 h post hospital admission) compared to later nutritional support improve outcomes in polymorbid inpatients?** *Recommendation 8.1* *Early nutritional support (i.e. provided in less than 48 hours post hospital admission) compared to later nutritional support should be performed in polymorbid medical inpatients, as sarcopenia could be decreased and self-sufficiency could be improved (Grade of recommendation B) – strong consensus (95% agreement)* **9. Does the continued use of nutritional support after discharge compared to nutritional support during inpatient stay alone affect the outcomes of polymorbid inpatients?** *Recommendation 9.1* *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 (95% agreement)* *Recommendation 9.2* *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 quality of life.* *(Grade of recommendation B) – strong consensus (95% agreement)* *Recommendation 9.3* *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 (95% agreement)*
Monitoring	**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 inpatients receiving nutritional support?** *Recommendation 10.1* *Nutritional parameters should be monitored to assess responses to nutritional support, while functional indices should be used to asses other clinical outcomes (i.e., survival, quality of life) in polymorbid medical inpatients.* *(Grade of recommendation B) – strong consensus (95% agreement)* **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 inpatients receiving nutritional support?** *Recommendation 11.1* *In polymorbid medical inpatients with reduced food intake and hampered nutritional status at least 75% of calculated energy and protein requirements should be achieved in order to reduce the risk of adverse outcomes.* *(Grade of recommendation B) – strong consensus (100% agreement)* *Recommendation 11.2* *Energy and protein fortified foods can be used in order to reach those relevant energy and protein targets in polymorbid medical inpatients.* *(Grade of recommendation 0) – strong consensus (100% agreement)*
Procedure of intervention	**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 inpatients?** *Recommendation 12.1* *Organizational changes in nutritional support provision should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition. In particular, interventions that ensure the provision of fortified menus for at-risk patients, establishing a nutrition support team and the use of multi-disciplinary nutrition protocols should be implemented.* *(Grade of recommendation B) – strong consensus (100% agreement)*
Non-PICO questions, under section "Discussion"	**a) Does underlying disease have an impact on expected outcome from nutritional support?** *Statement a.1*

(*continued*)

Topic	Clinical question and recommendation(s)/statement(s)
	The severity of acute-phase response may be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention. *(Level of evidence 1+) – strong consensus (100% agreement)* *Statement a.2* *Inadequate nutritional intake is common, and patient factors contributing to poor intake should be considered in designing nutritional interventions. Energy and protein intake are frequently inadequate to meet requirements in most older acute medical inpatients, worsening malnutrition during hospitalization and leading to poor outcomes. Poor intake is associated with several common patient/environmental characteristics, such as disease severity, symptoms compromising intake, anorexia, bedridden, hospital routines, dietary habits and possible therapeutic diets adopted at home.* *(Level of evidence 4) – strong consensus (100% agreement)* **b) How long should nutritional support be given in order to have an impact on the clinical course in a polymorbid patient?** *Statement b* *Although there is evidence to recommend the continued nutritional support post-hospital discharge on polymorbid medical inpatients who are malnourished or at risk of malnutrition, the ideal duration of the intervention has not yet been determined.* *(Level of evidence 4) – strong consensus (95% agreement)* **c) Are there risks of polypharmacy and drug-nutrient interaction in polymorbid inpatients?** *Statement c* *In polymorbid medical inpatients there is an important possibility of drug-drug or drug-nutrient interactions that needs to be taken into account, by establishing a pharmacist-assisted management plan for any interactions.* *(Level of evidence 3) – consensus (90% agreement)*

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" [1]. In fact, we do 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.

Polymorbidity is highly prevalent, affecting more than 70% of the hospitalized adult population, and is associated with higher mortality and healthcare burden [4]. Other consequences of polymorbidity include disability, functional decline, poor quality of life (QoL) and higher healthcare costs [3]. Whilst the prevalence increases with age, more than half of all people affected with this problem are younger than 65 years [5]. 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 [5]. 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 [6]. 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 a consensus on how to provide nutritional support for the polymorbid medical inpatient population.

2. Materials and methods

2.1. Pragmatic definition of polymorbidity for the current project

Guideline development is based on clinical trials that investigate the effects of screening and 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 inpatient population was established as:

- at least 2 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 or, alternatively
- a mean number of diseases or drugs (medications) over 1.5

In many studies, only this information is provided instead of the list of comorbidities and the proportion of the study population affected by each disease.

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" [7]. Additionally, it has been shown that the greater the number of medications, the higher the risk of weight loss [8], 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 [9].

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 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 2).

2.2. Guideline development

The guideline WG was composed of a multidisciplinary team of 15 European specialists in nutritional support, who are the authors of the current paper. Following the standard operating procedures for the development of ESPEN guidelines [10], the guideline WG had an initial meeting in Zurich, in January 2015, to discuss the several stages of this project, and to define all of the clinical

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 2 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 2 co-occurring diseases
Outcomes	Nutritional outcomes (e.g. weight, energy and protein intake) Clinical outcomes (e.g. mortality, infections) Patient-centred outcomes (e.g. quality of life) Healthcare resources	
Language and year	English; no restriction on publication year	

questions as well as the inclusion and exclusion criteria (Table 1). Other relevant clinical questions which could not be developed in the "PICO" format (i.e. containing the 4 elements of population of interest, interventions, comparisons and outcomes (PICO)) have been included in the discussion.

Twelve questions in the PICO format covering nine topics of nutritional support (indication, route of feeding, energy and protein requirements, micronutrients requirements, disease-specific nutrients, timing, monitoring, and procedure of intervention) were developed by the WG. These questions, the search key words proposed for each question, and the inclusion and exclusion criteria were discussed within the WG, and later approved by the ESPEN Guidelines Editorial Board (GEB).

A systematic literature search was conducted, first in secondary sources by searching published guidelines (e.g. from the National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network (SIGN), the American Society for Parenteral and Enteral Nutrition) and systematic reviews potentially relevant for each question, followed by a search in primary sources. This primary sources search was conducted by the same author in three databases (Medline, Embase and the Cochrane Library), until April 2016, using the GEB approved search terms proposed for each question. An example of a search strategy used can be found in Appendix 1 ("Search strategy used for question 2 in the Cochrane Library").

For each question, the results from each database were combined and exported to Endnote, followed by removal of duplicates and exportation to a Word document, allowing a single person (one of the WG coordinators) to undertake the screening of the final number of abstracts, in a standardized and systematic way.

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 = 32), the authors were contacted and requested to provide more information, which was usually to clarify whether their study population suffered from multiple comorbidities. For those studies whose authors could not be reached (n = 17), 11 were included and 6 excluded, as per the WG consensus decision.

Each WG member was allocated with one clinical question 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 [11], as exemplified in Tables 2 and 3.

A total of 4532 abstracts were screened. The details of the primary searches can be found in Table 4.

Thirty-eight studies were analyzed and included for the development of the recommendations. 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 2 ("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 22 recommendations and 4 statements (approved by the WG and the GEB office), which was followed by the start of the consensus procedure, by sending that draft to the members of the ESPEN guideline project for online voting (Delphi method) in February 2017. The results of this online voting were a strong consensus (agreement of >90%) in 68% of recommendations and 75% of statements, and consensus (agreement of >75–90%) in 32% of recommendations and 25% of statements. None of the recommendations or statements reached an agreement of below 75%.

The feedback received during the online voting was used to modify and to improve the recommendations in order to reach a

Table 2
Levels of evidence (SIGN grading system) [11].

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

Table 3
Grades and forms of recommendations (SIGN grading system) [11].

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

higher degree of acceptance at the final consensus meeting. The revised text was sent to the GEB office for approval.

The recommendations and statements with an agreement equal or lower than 90% were discussed in the final consensus meeting (organized by ESPEN), which took place in Frankfurt/Main, Germany, on the 24th April 2017. The consensus meeting was attended also by was attended by Cees Smit (Patient advocate, European Genetic Alliances Network (EGAN). After the voting, all of the selected recommendations were discussed and amended as required, and consensus greater than 89% was reached for all of the recommendations.

3. Results

A summary of all of the clinical questions and the recommendations, including the grade of recommendation and level of consensus achieved at the final consensus conference, is presented in appendix 3 ("supplementary data: summary of clinical questions and recommendations").

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

Recommendation 1.1.

In polymorbid medical inpatients, a quick and simple nutritional screening method using different validated tools should be applied to identify malnutrition risk. In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to consent an early adequate nutritional therapy and to define quality outcome measures of success.

Grade of recommendation B – strong consensus (100% 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 [12–14]. 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 [15]. Scoring systems for determining nutritional risk, such as the Nutritional Risk Score 2002 (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 [16–19]. Both of these tools are rapid, easily undertaken and show a high degree of content validity and reliability, thereby making them suitable in polymorbid inpatients including those patients with cognitive dysfunction [20,21]. If patients screen positive a more detailed assessment should be performed and a treatment plan should be developed. 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.

Table 4
Number of abstracts retrieved for each question, in each database, and number of studies included for analysis.

	Number of abstracts found in:				Included studies
	Medline	Embase	Cochrane Library	Total (without duplicates)	
Question 1	369	737	381	1401	2
Question 2	188	267	183	404	11
Question 3	318	532	327	859	1
Question 4	114	156	26	189	1
Question 5	162	220	82	395	2
Question 6	3	8	2	13	0
Question 7	116	174	102	223	2
Question 8	349	462	282	598	2
Question 9	6	4	10	19	10
Question 10	61	95	141	260	2
Question 11	18	23	7	25	2
Question 12	89	93	28	146	3

In a controlled trial, Rypkema et al. demonstrated that a standardized, early nutritional intervention in older polymorbid 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 intervention group (IG) vs. −0.76 ± 0.28 kg in the control group (CG), $p < 0.001$) and a significant lower rate of nosocomial infections (23.6% vs. 36.7%, $p = 0.01$) [22] **(Level of evidence 2+)**.

In a prospective, non-randomized cohort study, Jie et al. found nutritional support was beneficial for polymorbid inpatients at nutritional risk as defined by the NRS 2002 [13] **(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% versus 28.1%, $p = 0.009$), primarily because of the lower rate of infectious complications (10.5% versus 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 inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements (ONS), with or without nutritional counseling, versus no ONS, improve outcomes?

Recommendation 2.1.

In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely reach their nutritional requirements orally, ONS high in energy and protein shall be considered to improve their nutritional status and quality of life.

Grade of recommendation A − strong consensus (95% agreement)

Commentary:

Provision of ONS high in protein and energy in acutely ill hospitalized patients or inpatients at risk of developing malnutrition has been found to improve nutritional status. Hegerova el al. conducted a prospective randomized controlled trial (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, $p = 0.528$) [23] **(Level of evidence 1++)**. This supplementation resulted in significant preservation of muscle mass (lean body mass difference between admission and 3 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 3 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.

Gariballa et al. found in a double blind RCT with 445 hospitalized patients that ONS provision significantly improved nutritional status (as indicated by the significant increase in serum albumin, red-cell folate and plasma vitamin B12 concentrations of the IG) and reduced the number of non-elective re-admissions in the 6-month follow-up period (adjusted HR 0.68, 95% CI 0.49–0.94) [24] **(Level of evidence 1++)**. Similar results were also shown in other RCTs, where ONS provision (in addition to oxandrolone provided to both intervention and control groups) resulted in improvements of several parameters used to assess nutritional status, which were dependent on the level of DRM [25] **(Level of evidence 1−)**. Moreover, according to Starke et al., individualized nutritional support which included the provision of ONS in malnourished medical hospitalized patients resulted in improvement of their nutritional status (mean weight change from admission to discharge was 0.0 ± 2.9 kg in the IG vs. −1.4 ± 3.2 kg in the CG, $p = 0.008$) and quality of life (Short Form-36 function summary scale was 37 ± 11% in the IG vs. 32 ± 9 in the CG %, $p = 0.030$), and reduction of complications during their hospital stay (4/66 in the IG vs. 13/66 in the CG, $p = 0.035$) [19] **(Level of evidence 1++)**. According to Volkert et al., provision of ONS to malnourished geriatric hospitalized patients resulted in improvements in nutritional status (e.g. in the IG with good acceptance, the mean weight gain was +0.4 kg, when compared with a loss of −1.6 kg in the IG with poor acceptance and −0.1 kg in CG) and recovery rate (e.g. in the IG with good acceptance, the proportion of independent patients (BI score >65 points) increased from 36% at admission to 63% at discharge and to 72% after 6 months, and was significantly higher compared to CG at discharge (19%, $p < 0.05$) and after 6 months (39%, $p < 0.05$)) [26] **(Level of evidence 2+)**. Lastly, according to Potter et al., in a RCT of 381 malnourished older hospitalized patients, the provision of ONS resulted in a reduction in unintentional weight loss ($p = 0.003$), as well as in mortality (14.7% in the IG vs. 35% in the CG, $p < 0.05$) when the analysis was confined to the severely undernourished group [27] **(Level of evidence 2++)**.

Recommendation 2.2.

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutrient-specific ONS should be administered, when they may maintain muscle mass, reduce mortality or improve quality of life.

Grade of recommendation B − consensus (89% agreement)

Commentary:

Several specialized nutrient specific ONS have been tested for their effectiveness on the improvement of outcomes in hospitalized patients. According to the NOURISH study, a multicenter RCT which included 652 malnourished inpatients, high protein − β-Hydroxy β-Methylbutyrate (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 0.27–0.90), $p = 0.018$) [28] **(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 effect on their cognitive performance but with a significant positive effect on their self-reported quality of life (i.e. the treatment effect in quality-of-life scores using the SF-36 form at 6 months was 7.0 (95% CI 0.5–3.6), $p = 0.04$ for physical function, 10.2 (95% CI 0.1–20.2), $p = 0.047$ for role physical, and 7.8 (95% CI 0.0–15.5), $p = 0.05$ for social function domains, compared to placebo) [29,30] **(Level of evidence 1++ for both)**. Although these results are interesting and promising, the available studies remain limited.

Recommendation 2.3.

In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely reach their nutritional requirements orally, ONS should be considered as a cost-effective way of intervention towards improved outcomes.

Grade of recommendation B − strong consensus (95% agreement)

Commentary:

Early detection and intervention against DRM has been shown to improve nutritional status and reduce complications during hospital stay [19] and non-elective re-admissions [24,28] **(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% [31] **(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 0.91–1.17) for the overall group and 0.78 (95% CI 0.46–1·35) in the small undernourished subgroup). This stresses the importance of focusing nutritional support on those most in need [32] **(Level of evidence 1++)**.

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

Recommendation 3.1.

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

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 [33]. 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 [34,35]. Several randomized studies have compared the effect of nutritional support on outcomes of medical inpatients. A recent meta-analysis incorporating 22 RCTs conducted in medical inpatients found a significantly higher energy and protein intake, as well as beneficial effects on weight when comparing nutritional IG (including counseling and oral and enteral feeding) to CG [36]. When the analysis was restricted to the subgroup of malnourished patients, those receiving nutritional interventions had lower risk for readmission and shorter hospital stays, but no significant effect on mortality, infections and functional outcomes was found. Other studies also used nutritional strategies with EN and/or PN compared to usual care or other feeding strategies in the medical inpatient setting [37–39]; 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 [40] and patients with acute pancreatitis [41,42], there is some observational evidence for the polymorbid medical inpatient population [13]. This observational evidence [13] 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 score, that investigated the outcomes of patients receiving either EN or PN to patients without nutritional support [13] (**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 0.38–0.77), $p < 0.001$ and adjusted OR 0.42 (95% CI 0.27–0.64), $p < 0.001$, 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 were 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 the 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 und the 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.

Although outside the scope of these guidelines, there is some evidence from critical care demonstrating that EN compared to PN results in lower complication risk; nonetheless, a recent meta-analysis including 30 RCTs did not find a mortality benefit [40]. In that meta-analysis, EN had a lower risk of both infectious complications (risk difference 8.8, 95% CI 0.0–17.5) and non-infectious complications (risk difference 12.2, 95% CI 4.6–19.9) in the subgroup of medical critical care patients. Similarly for pancreatitis, a meta-analysis including 6 trials found that compared with PN, EN was associated with a significantly lower incidence of pancreatic infection complications (RR = 0.556, 95% CI 0.436–0.709), multi-organ failure (RR = 0.395, 95% CI 0.272–0.573), surgical interventions (RR = 0.556, 95% CI 0.436–0.709), and mortality (RR = 0.426, 95% CI 0.238–0.764) [37].

In summary, high-quality randomized studies comparing EN and PN 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 patients, 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.

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

Recommendation 4.1.

Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula.

Grade of recommendation 0 − strong consensus (96% agreement)

Recommendation 4.2.

In the absence of IC, total energy expenditure (TEE) for polymorbid older patients (aged >65 years) can be estimated using the formula 27 kcal/kg actual body weight. Resting energy expenditure (REE) can be estimated using the formula 18–20 kcal/kg body weight with the addition of activity or stress factors to estimate TEE.

Grade of recommendation 0 − strong consensus (95% agreement)

Recommendation 4.3.a)

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

Grade of recommendation 0 − consensus (agreement 89%)

Recommendation 4.3.b)

This target of 30 kcal/kg 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 (agreement 100%)

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 indirect calorimetry (IC) and for TEE the gold standard is doubly-labeled water. However, these methods are rarely available in the clinical setting and require considerable expertise [43]. Practitioners therefore tend to rely on either published prediction equations (e.g. Harris–Benedict [44] or Ireton-Jones [45]) 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 [46]. In the absence of indirect calorimetry 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 [47,48]. More than 200 prediction equations have been published in the literature, with accuracy rates ranging from 36% to 75% when compared with indirect calorimetry and no single equation emerges as being the most accurate in polymorbid medical inpatients [47]. 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 [49] 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 [50].

In a review designed to determine the energy requirements of frail older people [51], including polymorbid patients, 33 studies (2450 subjects) were identified where REE was measured by indirect calorimetry 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 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 [52]. 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.

In a study designed to evaluate the accuracy of prediction equations against IC in hospitalized patients [47], 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 [44,45,53] 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.

In a study designed to determine the energy requirements of severely underweight hospitalized patients [54] energy expenditure was measured by IC in 14 patients. 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.

This 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 [55].

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.

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 4.2. 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 [56] and PN [57] for geriatric patients.

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

Recommendation 5.1.

Polymorbid medical inpatients requiring nutritional support shall receive a minimum of 1.0 g of protein/kg of body weight per day in order to prevent body weight loss, reduce the risk of complications and hospital readmission and improve functional outcome.

Grade of recommendation A − strong consensus (95% agreement)

Commentary:

One high quality RCT [19] (**Level of evidence 1++**) and a subsequent secondary analysis of the same data [58] (**Level of evidence 1++**) compared the effect of protein intakes of 1 g/kg of patient's body weight per day versus lower intakes.

The trial by Starke et al. included adult patients hospitalized in a general medical ward, with a NRS score of 3 or more. The IG received 1 g of protein/kg of body weight per day in the form of individual food supply, fortified meals, in-between snacks and oral nutritional supplements for an average of 17.0 (±10.4) days. The control group received standard nutritional care for an average of 18.6 (±17.1) days, with a mean protein intake of 0.7 g/kg of body weight per day.

At discharge, patients receiving 1 g of protein/kg of body weight per day (and significantly more energy) experienced less weight loss (0.0 (±2.9) kg vs. −1.4 (±3.2) kg, $p = 0.008$), had an improved functional status (SF-36 function summary scale (37 (±11) % vs. 32 (±9) %, $p = 0.030$), a lower risk for complications (4/66 vs. 13/66, $p = 0.035$) and a reduced number of antibiotic therapies (1/66 vs. 8/66, $p = 0.033$), compared to the CG patients receiving less protein [19]. Drommer and colleagues confirmed that the number of complications was inversely correlated with the mean daily protein intake ($p = 0.017$). After 6 months, patients from the IG were less frequently readmitted to the hospital compared to the patients from the CG (17/64 vs. 28/61, $p = 0.027$) [19].

Although these analyses were both undertaken using the same RCT patient data, the strong design and high methodological quality supports the recommendation to provide at least 1 g of protein per kg of body weight in polymorbid inpatients. Recent guidelines from the American College of Gastroenterology about nutritional therapy in the adult hospitalized patients [41] suggest that protein targets as high as 1.5–2.0 g/kg body weight per day may even be needed to optimize nutritional support. In another recent publication evaluating practical procedures for nutritional support of medical inpatients, the authors investigated the question of protein intake targets needed to improve patients' outcomes. They used studies included in existing recommendations for particular diseases and medical specialties [34]. They also concluded that a minimum of 1.2 g of protein per kg of body weight per day is suitable for the vast majority of patients hospitalized in medical wards except for patients with renal impairment.

In the case of polymorbid medical inpatients with a renal condition, the amount of protein included in the daily nutritional plan may be different and should be cautiously assessed. Guidelines for renal patients recommend to lower the protein intake to 0.8–1 g/kg of body weight per day for at-risk or malnourished medical inpatients with acute and chronic renal failure and without renal replacement therapy [34,59].

Our search did not yield any study assessing the effects of different protein intakes on outcomes of patients with clear evidence of kidney diseases in addition to one or several others. Therefore, it is not possible to know how the different diseases affecting polymorbid patients with a renal condition might interplay and to provide a recommendation in regard to protein intakes in polymorbid inpatients with a renal condition.

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

Recommendation 6.1.

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

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

Recommendation 6.2.

Polymorbid medical inpatients exclusively fed orally with documented or suspected micronutrient deficiencies should be repleted.

Grade of recommendation GPP − strong consensus (93% 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. 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 of vitamin B12, folate and/or vitamin B6, even though the same subjects had apparently normal reported levels of the same micronutrients [60]. A study by Kilonzo et al. [61] 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. 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 inpatients due to the potential for any deficiencies to affect multiple and already compromised organ systems.

No studies were identified that reported the supplementation of multivitamins (with or without trace elements) compared to no supplements in polymorbid inpatients exclusively fed orally.

Question 7. Does disease-specific nutritional supplementation (e.g. fiber, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard formulations improve outcomes in polymorbid 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 [62]. 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 usable studies identified was extremely low.

Recommendation 7.1.

In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and β-hydroxy β-

methylbutyrate (βHMB) can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.

Grade of recommendation 0 − consensus (90% 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 anti-oxidant micronutrients). A RCT from Singapore which included 26 polymorbid patients hospitalized for more than 2 weeks [63] showed a marginal albeit significant effect of an arginine/glutamine/βHMB mixture on the healing of pressure ulcers (greatest improvement of viable tissues at 2 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 enterally) was likely responsible for the beneficial effects observed.

Other positive studies have been published using an oral nutritional supplement enriched in arginine, zinc and anti-oxidants in patients outside the scope of these guidelines [64,65].

Recommendation 7.2.

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

Grade of recommendation 0 − strong consensus (95% 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 [66] 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).

Recommendations 7.1 and 7.2 were downgraded from grade of recommendation B to 0, due to the limited amount of available studies.

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 inpatients?

Recommendation 8.1.

Early nutritional support (i.e. provided in less than 48 h post hospital admission) compared to later nutritional support should be performed in polymorbid medical inpatients, as sarcopenia could be decreased and self-sufficiency could be improved.

Grade of recommendation B − strong consensus (95% 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. Critically ill patients have been extensively studied, but still there is controversy. A recent meta-analysis conducted in populations with acute pancreatitis demonstrated that early EN was associated with significant reductions in infections, catheter-related septic complications, hyperglycemia, length of hospitalization and mortality, but the studies included did not show evidence of polymorbidity [67]. In one of the "Feed Or Ordinary Diet" trials [68], early tube feeding, defined as "as soon as possible", vs. avoiding any enteral tube feeding for at least 7 days, was associated with an absolute reduction in risk of death but again, it is not known whether this population (where stroke was the primary insult) was polymorbid.

From the available literature addressing this question in medical inpatient populations with confirmed polymorbidity, two studies were identified.

First, a prospective RCT from Heregova et al. [23] aimed to determine whether early nutritional therapy and exercise would influence the development of sarcopenia and impaired self-sufficiency during acute illness. Two hundred inpatients >78 years old were randomized to a CG receiving standard treatment or to an IG, which consisted of ONS (600 kcal, 20 g/d protein) added to a standard diet and a simultaneous intensive rehabilitation program from day 1 of hospitalization. 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 control group but only 0.4 kg lower in the treated group. Lean body mass did not reach its original value even 12 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 Barthel index), 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+**).

Second, Zheng et al. [69] 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−**).

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.

Recommendation 9.1.

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 (95% 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 [70]. Therefore, ensuring adequate nutritional intake during the transition from hospital to home is an important goal in malnourished patients. Recent systematic reviews found evidence for improved body weight and nutritional status in older patients after discharge either with individualized nutritional support [71] or intervention with ONS [72]. 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 or older 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) [73] **(Level of evidence 1−)**. Similarly, in a prospective RCT of 80 patients aged 75 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 [74] **(Level of evidence 1++)**.

Similar results were obtained in other RCTs. In a RCT of malnourished hospital inpatients (47 in the IG and 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 "Malnutrition Universal Screening Tool" score (−2.457 (±1.39) in the IG vs. −1.170 (±1.67) in the CG, p < 0.001) after 6 months of continued nutritional counseling by case manager nurses (frequency of visits depending on severity of malnutrition, either every month or every second month) [75] **(Level of evidence 1−)** and similarly, in a RCT of malnourished patients (according to the MNA-sf) aged 85 ± 6 years, individualized nutritional support for 4 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 [76] **(Level of evidence 1+)**.

Recommendation 9.2.

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 quality of life.

Grade of recommendation B − strong consensus (95% 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 hand grip strength 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 or older admitted to an acute hospital for medical or surgical conditions, 3-month nutritional intervention (with energy and protein rich diets, ONS and calcium + Vit D supplements, providing 600 kcal/day and 24 g protein/day as well as 400 IE vitamin D3 and 500 mg calcium) resulted in a reduction in the number of falls (10% vs. 24%, p = 0.02) [77] **(Level of evidence 1++)**, significant improvement in self-reported functional limitations (mean difference −0.72, 95% CI −1.15 to −0.28) [78], and was neutral in financial cost [79] **(Level of evidence 1++)**. On the other hand, increase in QoL did not differ between IG and CG receiving standard care [79] **(Level of evidence 1++)**. In the study by Persson et al., which included old patients at risk of malnutrition (85 ± 6 years), treatment with complete or incomplete liquid supplements (providing an average intake of 60 kcal and 11.25 g protein per day) and dietary advice for 4 months resulted in improvement of Katz activities of daily living index (p < 0.001; p = 0.05 between the groups), but not in QoL assessed by the 36-Item Short Form Health Survey [76] **(Level of evidence 1+)**. On the other hand, Casals et al. reported significantly improved QoL scores (assessed by the Short Form 12 Health Survey, being the difference between IG and CG 13.72, p < 0.001)) after 6 months of individualized nutritional support [75].

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 3 months was 0.128 (95% CI 0.095–0.161) in the IG vs. 0.067 (95% CI 0.031–0.103) in the CG) [80] **(Level of evidence 1+)**. Grip strength 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)) [81] **(Level of evidence 1+)**.

Recommendation 9.3.

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 (95% 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 (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 3 months compared to the CG patients who received a placebo (4.8% in the IG vs. 9.7% in the CG, p = 0.018) [28] **(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 6 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 [73].

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation

9.3 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 [56] and PN [57] for geriatric patients.

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.

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 inpatients receiving nutritional support?

Recommendation 10.1.

Nutritional parameters should be monitored to assess responses to nutritional support, while functional indices should be used to asses other clinical outcomes (i.e., survival, quality of life) in polymorbid medical inpatients.

Grade of recommendation B − strong consensus (95% 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.

Mendehall et al. [25] studied 271 polymorbid 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). Both groups initiated the nutritional support during hospitalization (30 days) and continued it at home when discharged (90 days). During hospitalization, patients in both groups were offered an identical hospital diet providing approximately 2500 kcal/d. Nutritional (i.e., body weight, triceps skinfold thickness), functional (i.e., handgrip strength) and clinical (i.e., laboratory tests) assessments were performed at baseline, after 1 month of hospitalization and after 2 months of outpatient therapy. Mendehall et al. also performed survival analysis at 6 months (i.e., 3 months after completion of nutrition therapy). All patients in both groups were malnourished. 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 handgrip strength 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 handgrip strength 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. [81] 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 oral nutritional supplement (IG) whereas the other group received only dietary counseling (CG group). At baseline, no difference was observed in nutritional (i.e., Subjective Global Assessment (SGA), body composition) and functional parameters (i.e., peak flow, handgrip strength) as well as in QoL (i.e., 36-item short form questionnaire) between the two groups. At the end of the study, both body weight and body cell mass improved significantly in both groups. However, handgrip strength (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 QoL subscales of 36-item short form questionnaire ($n = 8$) significantly improved in IG patients, whereas only three (physical functioning, bodily pain and vitality) improved in CG patients. Of interest, the change in handgrip strength correlated with the change in two 36-item short form questionnaire physical scales (i.e., physical functioning and physical role). By applying the reasoning used for Mendehall et al.'s trial, 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. [82] 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. then concluded that based on their analysis, changes in nutritional markers do not predict clinical outcomes. More recently, Jeejeebhoy et al. [83] 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 of length of stay. SGA C and hand grip strength but not food intake were independent predictors of 30-d readmission. This very recent 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 inpatients receiving nutritional support?

Recommendation 11.1.

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

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

Recommendation 11.2.

Energy and protein fortified foods can be used in order to reach those relevant energy and protein targets in polymorbid medical inpatients.

Grade of recommendation 0 − strong consensus (100% agreement)

Commentary:

In polymorbid medical inpatients reduced food intake is more the rule than the exception [84] and is often an important part of the complex symptomatology that forces the patient to the hospital. Reduced food intake has several commonly occurring pathophysiologies including anorexia/reduced appetite, dysphagia or oral and dental problems. When reduced food intake is chronic or severe over longer and shorter periods of time, respectively, weight loss and malnutrition ensues. Since weight loss with malnutrition and reduced food intake are so closely linked it may be difficult to

distinguish which of the syndromes are most detrimental for the patient. 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 [85,86]. 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 [87]. This energy intake was cross-sectionally associated with an increased risk of infections; adjusted odds ratio being 2.26 (95% CI 1.24–4.11).

In a good quality prospective observational study [88] (**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 2.8–22.6) and 2.9 (95% CI 1.4–6.1), respectively.

Similar results were observed in a supportive study conducted in the critically ill population [89]. Twenty-eight 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 indirect calorimetry and protein target calculated as 1.2–1.5 g/kg body weight/day. The group of the patients who received 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.

Thus, observational cohort studies clearly indicate that achieving goals for energy and protein intake during hospital stay is associated with better clinical outcomes. Such studies are unable to indicate whether or not the clinical outcome would be improved if sufficient nutrition could be provided. Such evidence can only be achieved by RCTs. 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. 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, it is sometimes suggested (on expert opinion ground) 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.

We aimed at finding studies that could answer the question: Does meeting more than 75% of energy and or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid inpatients receiving nutritional support? For this reason, we looked for RCTs in the literature. Unfortunately, no such studies were found. However, a Danish RCT [90] 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 patients 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 control group. Handgrip strength 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.

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 inpatients?

Recommendation 12.1.

Organizational changes in nutritional support provision should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition. In particular, interventions that ensure the provision of fortified menus for at-risk patients, establishing a nutrition support team and the use of multi-disciplinary nutrition protocols should be implemented.

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 studies have suggested that changes to the organization of nutritional support for in-patients may improve outcomes. One cohort study implemented the use of nutritional healthcare assistants. Medical patients who were deemed at high risk of malnutrition by the NRS 2002 were allocated a nutritional healthcare assistant, who was responsible for ensuring they received any necessary assistance to eat and drink and prepared individual meals for them. This study did not evaluate the impact on nutritional outcomes; however, the patient's perception of their nutritional care was improved and food wastage reduced [91]. Food fortification implemented in a non-randomized trial with medical, orthopedic and older inpatients, showed an increase in energy intake of 17.5% ($p = 0.007$) over a 3-day recorded period [92]. Furthermore, collated results from three cross-sectional studies reported as one paper have suggested that introducing a nutrition screening tool and making changes to catering services may lead to a reduced prevalence of DRM across the general hospital population [93]. In this study, the investigators devised their own local nutrition screening tool as none was used at their organization prior to the intervention.

Despite these interesting studies in non-polymorbid patients, a systematic review of non-randomized studies showed that improvements are not consistently demonstrated. Forty-one studies were included in the review considering changes to the organization of nutrition services, feeding environment and meal modification in hospital in-patients or those living in residential care. Due to the variability in reporting outcomes, it was not possible to assess the beneficial effects of specific interventions [94]. Therefore, it is important to consider the specific impact of organizational changes on polymorbid medical inpatients. From the identified literature, three studies were found. A single-blinded RCT [90] demonstrated how the use of a protein fortified menu was effective in increasing the protein intake of patients. Eighty-four patients were randomized to the study with a completion rate of 96%. The intervention group was able to choose from a protein enriched menu in addition to the standard hospital menu. The control group received the standard hospital menu. Patients were monitored for seven days. There was no significant difference in energy intake, length of stay or handgrip strength between the groups. However, mean protein intake was significantly increased in the IG; with 27/41 compared to 12/40 in the CG meeting $\geq$75% protein

requirements ($p = 0.001$). Protein requirements were set at 18% of total energy requirements. Energy requirements were calculated by using the Harris–Benedict equation to estimate basal metabolic rate, which was then multiplied by a stress/activity factor according to Danish guidelines **(Level of evidence 1+)**.

A further, prospective controlled trial [22] involving 298 polymorbid geriatric inpatients, demonstrated the use of an early multidisciplinary intervention protocol. The protocol included activities such as nutrition and dysphagia screening, ensuring better patient positioning for mealtimes 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 (average 0.9 kg) was observed in the IG whereas a weight loss (average 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+)**.

Finally, a cohort study [95] demonstrated the impact of a nutrition support team on the management of patients requiring, or referred for, PN. Though the primary aim was to show cost-savings with nutrition support team management of PN, secondary clinical outcomes were also measured. Following a nutrition support team-lead, structured teaching program for nursing staff the catheter related sepsis rate in PN patients fell 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 nutrition support team assessment and rapid instigation of enteral feeding. **(Level of evidence 2+)**. Thus, the evidence shows that organizational changes in nutritional support provision can reduce the risk of adverse outcomes in polymorbid medical inpatients.

4. Discussion

Although the key areas of nutritional support in polymorbid medical inpatients were covered by the development of questions in the PICO format, there were a few clinical questions particularly relevant for the polymorbid inpatient population that were also developed by the WG but unable to be transformed into the required PICO format. These questions are presented below, with proposed statements (which were subjected to voting) and supportive text. These statements are informative points of the evidence rather than guides for action (i.e. they are not recommendations).

a) **Does underlying disease have an impact on expected outcome from nutritional support?**

Statement a.1.

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

Level of evidence 1+ – strong consensus (100% agreement)

Statement a.2.

Inadequate nutritional intake is common, and patient factors contributing to poor intake should be considered in designing nutritional interventions. Energy and protein intake are frequently inadequate to meet requirements in most older acute medical inpatients, worsening malnutrition during hospitalization and leading to poor outcomes. Poor intake is associated with several common patient/environmental characteristics, such as disease severity, symptoms compromising intake, anorexia, bedridden, hospital routines, dietary habits and possible therapeutic diets adopted at home.

Level of evidence 4 – strong consensus (100% agreement)

Commentary:

There are two main challenges in answering this question. One is the validity and reliability of nutritional assessment in acutely ill aging patients; the other is to understand if the relationship between poor nutritional status and acute-phase response is causal or an association.

Gariballa et al. [96] published a study in 2006 investigating the effects of the acute-phase response on nutritional status and clinical outcome of hospitalized medical polymorbid patients. The study was conducted in 445 patients in a double-blind RCT of nutritional supplementation and participants had their nutritional status assessed from anthropometric, hematologic, and biochemical data at baseline, 6 weeks, and 6 months. Outcome measures including disability, length of stay, and 1-year mortality were recorded. C-reactive protein concentration, a marker of acute-phase response, was also measured. Multivariate analysis was used to measure the association between acute-phase response and nutritional assessment variables after adjusting for age, disability, chronic illness, medications, and smoking. This study concluded that the acute-phase response is associated with poor nutritional status and poor clinical outcome in older patients. Yet, there was still an unanswered question which was whether nutritional support removes or mitigates the hazard of poor outcome associated with the acute-phase response. Confirmation of the relationship between underlying disease and expected outcome from nutritional support will need larger interventional studies to determine the optimal timing and composition of nutritional therapy relative to a patient's metabolic state.

In another paper, Mudge et al. [97] conducted a prospective study of patient factors associated with inadequate nutritional intake in older medical polymorbid inpatients, including 134 medical inpatients ≥65 years old. Primary outcome was energy intake less than resting energy expenditure. Explanatory variables included age, gender, number of comorbidities, number of medications, diagnosis, usual residence, nutritional status, functional and cognitive impairment, depressive symptoms, poor appetite, poor dentition, and dysphagia.

b) **How long should nutritional support be given in order to have an impact on the clinical course in a polymorbid inpatient?**

Statement b.

Although there is evidence to recommend the continued nutritional support post-hospital discharge on polymorbid medical inpatients who are malnourished or at risk of malnutrition, the ideal duration of the intervention has not yet been determined.

Level of evidence 4 – strong consensus (95% agreement)

Commentary:

The ideal duration of post discharge nutritional intervention has not yet been determined but, in all likelihood, varies according to patients' age, underlying disease, initial nutritional status, type of nutritional support and endpoint of interest. In most RCTs on intervention with ONS, the sip feeds were given for three months [28,77–81], whereas individualized nutritional support (which might include ONS where necessary) was usually carried out for longer periods (e.g. 4 months in the study by Persson et al. [76], or 6 months in the studies of Feldblum et al. [73] or Casals et al. [75]). 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 [79]. Milne et al. also conclude in their systematic review on supplementation that the

duration of treatment is frequently too short to expect any improvement in QoL or physical activities in older adults [98].

c) **Are there risks of polypharmacy and drug-nutrient interaction in polymorbid inpatients?**

Statement c.

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

Level of evidence 3 – consensus (90% agreement)

Commentary:

Polymorbid 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. 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 co-morbidities in addition to human immunodeficiency virus infection [99,100] or psoriasis [101]. 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 [102] 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 [103]. 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 [104]. Advice on the complexities of all of these potential interactions in polymorbid 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 [1]. 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.

5. Conclusions

Despite the methodological difficulties in creating non-disease specific guidelines, we managed to review the evidence behind several important aspects of nutritional support for polymorbid medical inpatients. This resulted in the development of 22 practical recommendations and four statements intended to guide clinicians working with this patient population. 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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Conflict of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.06.025.

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