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

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

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

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

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

3.32. Recommendation 32

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

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

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

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

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

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

4. Conclusions

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