
Basics in Clinical Medical Nutrition

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Abstract

Nutrition is a basic requirement for life and plays an important role in health and in disease prevention, but malnutrition is a common event and a cause of increased morbidity and mortality, particularly in patients with disease-related malnutrition showing inflammation and a catabolic state. Malnutrition is often overlooked, and deterioration in the nutritional status following admission to hospital is common. It should be actively pursued by a ubiquitous system of nutrition screening, and full nutritional assessment is required for those found to be at risk. There are simple screening tools which can be used by all health care professionals. Assessment considers body composition, inflammatory status and other aspects of underlying diseases and their functional consequences; it is a more specialist process. It is important to determine the energy and protein needs of each individual patient. Appropriate nutritional intervention can often be offered by the oral route, using food with or without special supplements. When this is insufficient, enteral tube feeding will normally be sufficient, but there is an important subgroup of patients in whom enteral feeding is contraindicated or unsuccessful, and in these patients parenteral nutrition (either total or supplemental) is required. A number of immunonutrients and other special substrates have been shown to be helpful in specific circumstances, but their use is not without potential hazards, and therefore adherence to international guidelines is recommended.

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Introduction

Nutrition is a basic requirement for life. Accordingly, nutrition plays an important role in promoting health and preventing disease. Many reasons can lead to a weight change and malnutrition. Malnutrition is a condition resulting from a combination of varying degrees of under- or overnutrition and inflammatory

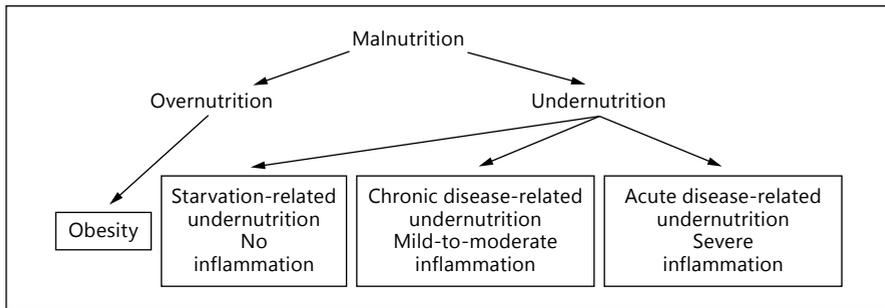


Fig. 1. Classification of energy and protein malnutrition.

activity, leading to an abnormal body composition [1]. Several classifications of malnutrition have been proposed in the past. For clinical settings, an etiology-based approach makes most sense. An international consensus committee has proposed the following new terminology:

- Starvation-related undernutrition
- Chronic disease-related undernutrition
- Acute disease- or injury-related undernutrition

In this etiology-based definition of malnutrition and malnutrition risk, the key role of inflammation in disease-related malnutrition is included (fig. 1) [2].

Patients with chronic starvation without inflammation (e.g. patients with anorexia nervosa) belong in the first category. Patients with a mild-to-moderate degree of inflammation can mostly be included in the second category (e.g. cancer, rheumatoid arthritis or sarcopenic obesity). Patients with acute and severe degrees of inflammation are regarded as members to the third category (e.g. patients with major infection, burns, trauma or closed head injury).

Patients with minor nutritional deficiencies and those with overt under- or overnutrition are common in clinical practice. The prevalence of malnutrition (undernutrition) among hospitalized adult patients ranges from 30 to 50%, depending on the criteria used, and in part whether those at high risk as well as those with established malnutrition are included [3, 4]. The EuroOOPS study, which included data from 26 hospital departments from 12 European countries, found that 32.6% of the patients were at risk for undernutrition [5]. Undernutrition should be seen as an additional disease, as well as an important component of comorbidity. The underlying condition and inadequate provision of nutrients (particularly energy and protein) are the main reasons for developing undernutrition. Many patients are already undernourished before they reach the hospital. Those at highest risk for undernutrition are elderly people who are hospitalized or living in care homes, people on low incomes, socially isolated people, patients with chronic disorders and patients recovering from a serious illness or condition, particularly a condition

that affects their ability to eat. In addition, hospitalized patients often show further deterioration in their nutritional status. One large survey showed that 4 of 5 patients do not consume enough to cover their energy or protein requirements [6]. There are many known reasons to explain this. The underlying disease may directly impair nutrition (e.g. in case of an esophageal stricture) and can induce metabolic and/or psychological disorders which increase the nutritional needs or decrease food intake. In addition, the fasting periods before many examinations and interventions lead to further inadequate food intake. Hospital undernutrition may also aggravate because of inappropriate meal services, inadequate quality and flexibility of the hospital catering, and insufficient aid provided by the care staff.

The consequences of undernutrition are well known. A poor nutritional status leads to an increase in complications, a longer hospital stay, higher mortality, higher costs and more hospital readmissions [5, 7]. The EuroOOPS study, for example, found significant increases in complications, length of stay and mortality in patients at risk for undernutrition [5]. Undernutrition also affects the efficacy of or tolerance to several key treatments, such as antibiotic therapy, chemotherapy, radiotherapy or surgery. Furthermore, it is now clearly demonstrated that undernutrition significantly increases overall health care costs [8].

Undernutrition is undoubtedly a major burden for patients and health care professionals, and active screening for malnutrition should be routinely performed. When undernutrition is diagnosed, it should be treated according to a nutritional care plan tailored to the individual patient. The best outcomes were obtained with supervision by a multidisciplinary nutritional support team.

To improve the overall outcomes from nutritional treatment, it is necessary to select patients with overt undernutrition and those at increased risk of developing nutritional deficiencies during their hospitalization. Ideally, all patients are screened during admission to hospital, followed by a detailed assessment of the nutritional status in those found to be at increased risk. In patients diagnosed with malnutrition or at high risk of malnutrition, an appropriate nutritional intervention should ensue. Unfortunately, although this process is well known and forms part of several national and international guidelines, it is not carried out everywhere. It remains necessary to raise the awareness of undernutrition and to improve the outcomes of treatments by nutritional interventions.

Nutritional Screening and Assessment

The identification of patients with nutritional deficiencies or overt undernutrition is the first step in nutritional support. In all patients, the nutritional status should be recorded within 2 days after admission to hospital.

Table 1. Screening tools

Malnutrition Universal Screening Tool (MUST)
Subjective Global Assessment (SGA)
Nutritional Risk Screening (NRS-2002)
Mini-Nutritional Assessment (MNA) (elderly)

The evaluation of the patient starts with a screening process. If the patient is found to be at increased risk, a detailed nutritional assessment should follow.

Nutritional Screening

Nutritional screening uses a tool designed to evaluate rapidly and simply if the patient is malnourished, at risk of malnutrition or if he or she will become undernourished. The screening method should be sensitive enough to detect almost all patients at risk of malnutrition. Several validated screening tools (table 1) are available and recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN).

Recently published guidelines for nutritional screening of individuals in the community, hospitalized patients and elderly patients living in institutions are available (www.espen.org).

Each of the most frequently used screening tools relies to some extent on four principal parameters:

- (1) Weight loss over time
- (2) Recent food intake
- (3) Current body mass index (BMI; kg/m²)
- (4) Severity of the primary disease

For general screening in the community, the Malnutrition Universal Screening Tool (MUST) is a simple tool for rapid estimation of the grade of the malnutrition risk [9]. Its main disadvantage is that the recent food intake is not included, and calculations of the percent weight loss and BMI have caused problems in some units. The most widely used screening tools in hospital are the Subjective Global Assessment (SGA) and the Nutritional Risk Screening (NRS-2002) [9–11].

For the SGA, first the patient's history is taken, followed by a physical examination [10]. The difficulty with the SGA is that it needs great experience in order to obtain reliable and reproducible results. The screener has to integrate all the information to make an overall judgement on the patient's nutritional status.

The NRS-2002 is a simpler and well-validated screening tool [11]. The NRS-2002 starts with questions about the four items listed above for an 'initial' screen-

ing. If any of the questions is answered with 'yes' and a marked difference from normal values is observed, a 'final' screening follows. The final screening includes documentation of the impairment in the nutritional status and the severity of the disease. For each parameter, a score from 0 to 3 can be given. A final score of 3 or more in this validation process indicates that the patient will benefit from nutritional support.

For patients aged 65 years or more, two specific and well-validated tools are available [12, 13]. The initial long version of the Mini-Nutritional Assessment (MNA) was followed by a simpler one. The short form of the MNA has turned out to be as good as the long version, but it takes less time. The MNA is a combination of screening and assessment tools.

A comparison of the tools for nutritional screening and assessment of patients during hospital admission showed that the NRS-2002 had a higher sensitivity and specificity than the MUST and compared to the SGA. There was a significant association between the length of hospital stay and the nutritional status and risk by the SGA, NRS-2002 and MUST [14]. On admission to hospital, all of these three instruments can be recommended. The most suitable can be chosen according to the preference and experience of the individual unit.

Nutritional Assessment

For some patients, screening is not enough, and a more detailed assessment is necessary. A nutritional assessment should be done in those patients found to be at risk during screening, and when metabolic or functional problems prevent the application of a standard plan. For a detailed nutritional assessment, the following three steps are recommended:

- (1) Measurement of body composition
- (2) Measurement or evaluation of inflammatory activity and disease activity
- (3) Measurement of functional parameters

Measurement of Body Composition

Body composition describes the body compartments, such as fat mass, fat-free mass, muscle mass and bone mineral mass, in percentage terms depending on the body composition model used. Body composition changes due to starvation, underlying disease and mobility/exercise. Several simple methods to measure body composition are available. Most often, the BMI is calculated by measuring height and body weight (BW). Low and high BMI values are associated with increased morbidity and mortality. The BMI does not, however, reliably indicate the distribution between lean mass and adipose tissue, as there is no linear relationship between BMI and body compartments. Individuals with a low BMI may have an increased fat-free mass; on the other hand, individuals with a high BMI

may have a disproportionately low fat-free mass (e.g. sarcopenic obesity), placing them at an increased risk of failing to overcome disease or trauma.

Anthropometric measurements of limb circumferences and skinfolds represent simple, noninvasive and inexpensive ways of assessing the nutritional status. While mid-arm circumference has been shown to reflect muscle mass, triceps skinfold thickness is considered to be an indicator of subcutaneous fat. Although the measurements appear relatively easy, considerable experience is required to obtain reliable results. There is wide interobserver variability.

Another method of measuring body composition is bioelectrical impedance analysis (BIA). BIA is also a simple, inexpensive and noninvasive method of estimating body composition. It is suitable for routine bedside measurements. It relies on the detection of the body's conductivity (typically between wrist and ankle), which differs according to the relative proportions of fat, muscle and water. BIA provides reliable data on total body water, body cell mass and fat mass in subjects without significant fluid and electrolyte abnormalities when the appropriate equations (correcting for age, sex and ethnicity) are used. BIA is not recommended in patients with an abnormal hydration state, in subjects with extreme BMI values (<16 or >34) or in the elderly. Extraneous electrical interference also makes BIA measurements less suitable for patients in the intensive care unit (ICU) [15, 16].

A new development in this field is the use of the bioelectrical impedance vector analysis. The position and the length of the vector provide information about the hydration status as well as body cell mass and cell integrity. Both undernutrition and obesity are clearly reflected by the vector analysis, making this approach an attractive bedside method to identify and monitor the patients' nutritional status, which is less likely than BIA to be confounded by the presence of edema or ascites.

More sophisticated methods for the study of body composition are dual-energy X-ray absorptiometry, magnetic resonance imaging (MRI) and computerized tomography (CT).

Dual-energy X-ray absorptiometry depends on the analysis of radiological density (usually in the hip and spine) and is a useful, indirect method to measure the volume of fat mass, fat-free mass and bone mineral mass (density). It is relatively inexpensive and increasingly used in clinical practice and research. The only drawback is a small radiation exposure. It is currently regarded as the gold standard by many authors.

MRI and CT can also be used for the assessment of body composition. MRI and CT allow not only the quantification of fat mass and fat-free mass, but also give information about the regional fat distribution and enable an estimate of the amount of skeletal muscle. The advantage of MRI over CT is that for MRI

nonionizing radiation is used. These two methods are mainly used in research because of their higher costs, the amount of time needed and their more limited availability [17]. However, it is often possible to obtain nutritional information from scans taken for general diagnostic purposes, and 'single slice' techniques reduce the time and costs for review scans. It is probable that MRI will soon be established as the new gold standard for the measurement of body composition.

For research, several other sophisticated methods are available. These include dilution methods, the measurement of total body potassium and in vivo neutron activation analysis. These techniques are demanding and expensive. Therefore, they are not used in clinical practice.

Measurement of Inflammatory Activity and Disease Activity

Inflammation affects both body composition, mainly the muscle mass, and function. Inflammation is characterized by the production and release of proinflammatory cytokines into the circulation; these cytokines are catabolic for muscles. C-reactive protein levels correlate closely with the release of interleukin-6 and can be used as an inflammatory marker. In addition, inflammation reduces albumin levels. Therefore, low albumin levels are not a good indicator for the nutritional status. Serum albumin levels reflect disease severity more closely and can be used as an outcome predictor [18]. Low serum albumin levels are associated with a higher rate of complications and mortality [19, 20]. Extensive laboratory testing is not recommended for the assessment of the nutritional status, but it does play an important role in monitoring nutritional interventions. For short-term outcomes, transferrin, transthyretin (prealbumin) or retinol-binding protein can be used because of their short half-lives. Albumin is more suitable for long-term outcomes because of its longer half-life [18].

Measurement of Functional Parameters

Testing of function is increasingly regarded as important in nutritional assessment, and indeed muscle strength as well as cognitive and immune functions, all influence the quality of life.

Muscle strength is a good functional parameter with which to predict the outcome of both acute and chronic diseases. Both muscle size and muscle inflammation are independent predictors, firstly of muscle strength and secondly of outcome. Typical measurement parameters of muscle strength are hand grip strength, knee extension, hip flexion strength or peak expiratory flow. Impaired hand grip strength has been shown to be a good predictor of increased postoperative complications, increased length of hospitalization, higher rehospitalization rates and a decreased physical status. In addition, it is an excellent predictor not only of short- but also of long-term mortality [21]. For the interpretation of single values,

adequate reference values have to be used. Walking distance in a given time period (e.g. 3 min) can also provide an objective measure of global function.

It is important to include a measurement of cognitive function such as mood, concentration and memory, for example, in a detailed assessment. There is however no established consensus on the tests which can most optimally be used. Only in the elderly and in some patients with liver disease are there simple practicable methods. For the moment, we necessarily rely on the clinical impression in most patient groups.

Immune function has been determined by testing skin reactivity to an array of antigens. The obtained results largely reflect the severity of the disease and, as such, give a crude 'yes' or 'no' answer to the question as to whether the immune function is compromised. It does not furnish a quantitative measure of immune function. In addition, lymphocyte counts generally indicate the degree of illness and do not reflect malnutrition properly. For the moment, the routine measurement of immune function is not recommended because of the very controversial results in current studies regarding its nutritional significance.

Nutritional Interventions

The nature of a nutritional intervention depends on the underlying disease and the nutritional status. When undernutrition is diagnosed or a patient is at risk of undernutrition, a nutritional intervention plan should be started concomitant with the treatment of the underlying disease causing it. Nutritional support is a stepwise process. The choice of an appropriate feeding regimen depends on the clinical situation. Several approaches can be considered. Nutritional counseling and specific oral diets (including oral supplements) can be helpful. In some patients, however, oral nutrition is not possible, so enteral or parenteral nutrition has to be initiated. Regardless of the administration route, the estimation of energy and protein requirements is always a very important issue.

If patients at nutritional risk have appropriate nutritional support, their outcome is improved and rehospitalization rates are decreased. Furthermore, their hospital stay is shorter, and their quality of life is increased [22]. Freely available guidelines (www.espen.org) can help to guide nutrition in specific diseases.

Oral Nutrition in Hospitals

Oral feeding should be tried first if there are no contraindications and the gastrointestinal tract is working properly. A variety of menus and diets targeting specific patients' categories and needs, including diets for vegetarians and different ethnic groups, are available for consideration. In addition, diets for spe-

cific diseases should be available (e.g. lactose- and gluten-free diets, and diets for patients with renal or hepatic diseases). The energy and protein intake can be improved by adding energy- and/or protein-rich supplements to the diet. Furthermore, high-energy snacks between meals can have beneficial effects. Oral intake can be further improved by a protected ‘meal time policy’, which includes three meal times free from avoidable and unnecessary interruptions. Also, the ambience where the meals are served has to be taken into account.

It is very important to monitor nutritional intake. Early detection of reduced nutritional intake is a key factor in the prevention of hospital undernutrition. Dietary protocols and supervision of the tray collection (e.g. four-quarter plate assessment) are useful. If the intake is not enough, oral nutritional supplements (ONS) can be included. ONS are liquid, semisolid or powder products containing the important macro- and micronutrients. ONS are available in a variety of flavors. They are energy dense, and contain 200–300 kcal per serving and 10–20 g protein/300 kcal per serving. ONS should be given in between the regular meals. It has been shown that ONS do not reduce voluntary food intake [23]. The major drawback of ONS is compliance. This has to be carefully considered, and action must be taken if the ONS are not (any longer) consumed in the prescribed amounts.

At present, the best approach seems to be an individual, multifactorial nutritional intervention program. It has recently been shown that such an approach, incorporating (inter alia) counseling, supervised eating and ONS, increases calorie and protein intake, maintains BW, decreases complications and readmission rates, and increases the quality of life [24].

Enteral and Parenteral Nutrition

In cases where oral nutrition is not possible for whatever reason, enteral and/or parenteral nutrition should be considered if a significant benefit for the patient can be anticipated.

Enteral Nutrition

The classical criteria for enteral nutrition are: preexisting severe undernutrition; oral intake less than 60% of estimated caloric requirements; delay before recovery of oral eating is expected to last more than 5–7 days, and absence of gastrointestinal, metabolic or circulatory contraindications. From the therapeutic, legal and ethical standpoints, enteral nutrition given by a tube is medical treatment.

Several parameters must be considered in the choice of an appropriate feeding tube (nasogastric/nasojejunal percutaneous endoscopic gastrostomy or fine-needle jejunostomy) and in the type of the formula. The type of tube depends on

the integrity of the gut function and the expected duration of feeding. Nasogastric or nasojejunal tubes are recommended for short-term feeding (<3 weeks), and percutaneous endoscopic gastrostomy or fine-needle jejunostomy for longer-term feeding (>3 weeks).

The choice of the formula depends on the underlying disease and the specific demands of the patient. Nutritional support is different in patients with undernutrition without inflammation from that in patients with chronic or acute inflammatory disease.

In patients with undernutrition and no inflammation, e.g. in anorexia nervosa cases, no specific formulae are necessary. Feeding should be started below the target level and slowly advanced to the calculated goal. These patients have a higher risk of the refeeding syndrome [25], so close observation and careful monitoring of electrolytes (particularly phosphate) is mandatory.

Patients with a chronic disease leading to undernutrition can benefit from several special enteral diets. For example, cancer patients need a high-protein diet and may benefit from anti-inflammatory substrates, such as ω -3 fatty acids and antioxidants [26]. Patients with chronic kidney disease who are not on dialysis should have a diet with lower amounts of protein and phosphorus. On the other hand, patients on dialysis benefit from a high-protein and low-phosphorus diet to compensate for the protein loss during dialysis. In patients with gastrointestinal dysfunction or inflammatory bowel diseases, diets with hydrolyzed proteins and medium-chain triglycerides are sometimes better tolerated than normal formulae [27]. Several guidelines showing how nutritional support can be improved in different patient groups have been published (e.g. ESPEN guidelines: www.espen.org).

In patients with acute disease, especially if they have to be treated in the ICU, nutritional support can be a challenge. Acute severe inflammation increases the resting-energy expenditure and nitrogen excretion. There is a strong catabolic drive, which rapidly affects the muscles. The consequent loss of lean body mass has a major influence on outcome. The worst outcomes are seen in acutely ill patients who were already undernourished before hospitalization. In all acutely ill patients, it is important to define the amounts of energy and protein required. Most of these patients are still underfed in the ICU. A global survey showed that calorie and protein administration reached only 44–52% of the amounts prescribed [28].

The gold standard to assess energy requirement is indirect calorimetry. Although it is the most appropriate method to answer this question, it is seldom used. Using the different predictive equations is also possible, but it has to be borne in mind that these equations often underestimate the caloric need. To overcome these problems, the ‘rule of thumb’ formula is often used. In this,

25–35 kcal/kg BW per day are recommended using the ideal BW for calculation. This simple approach has been shown to perform reasonably well in comparison with indirect calorimetry. For obese patients, the adjusted BW should be used. In the ICU, it is crucial not to under- or overfeed the patients. Several studies have shown that a calorie deficit over time increases morbidity and mortality [29, 30]. Equally, hyperalimentation, i.e. the administration of excess energy, predisposes to a fatty liver and also leads to a poorer outcome.

To improve outcome, it is crucial that not only the right amount of energy but also an adequate amount of protein is provided. It is a consistent finding that the amount of protein given to patients is too low, and that this deficit is proportionally greater than the deficit in energy supply. Patients in the ICU usually do not get more protein than 0.8–1.0 g/kg BW per day. Many observational studies have shown that outcomes can be improved by increasing protein supplements. Newer recommendations for protein prescription are accordingly higher, with a typical target value of 1.3–1.5 g/kg BW per day. Allingstrup et al. [31]. have nicely demonstrated that patients with a higher protein intake had a significantly better survival than those with a low protein intake. Weijs et al. [32] confirmed their results in another elegant study. They found that the 28-day mortality rate was only decreased in patients reaching both energy and protein goals. Currently, it is recommended that enteral nutrition should start as early as possible. Large studies have confirmed this by showing a significant effect on mortality in the early-fed groups [33, 34].

Parenteral Nutrition

Most of the published meta-analyses reported a benefit of enteral nutrition over parenteral nutrition. This is most obvious in respect of infective complication rates. Mortality is generally comparable for enteral and parenteral nutrition except in patients with severe undernutrition, where the parenteral route is more advantageous. Therefore, parenteral nutrition can be recommended in patients with severe undernutrition; in case of contraindications to enteral nutrition, or as a supplement if 60% of the estimated requirements cannot be reached by enteral nutrition by day 3. Therefore, it is very important to monitor energy and protein intake. Supplementation of missing calories by parenteral nutrition is then recommended. Two recently published studies confirmed this approach. In TICACOS (Tight Calorie Control Study), Singer et al. [35] found that providing the target energy requirement based on repeated energy measurements by indirect calorimetry was achievable in a general ICU and that it was associated with lower hospital mortality, although morbidity was increased. In an optimization study of energy provision with supplemental parenteral nutrition in crit-

ically ill patients, Heidegger et al. [36] demonstrated a significant reduction in nosocomial infections in the early supplemented group compared to the non-supplemented group (27 vs. 38%). In addition, the energy and protein intake was significantly higher, and the mechanical ventilation time was reduced (83 vs. 108 h). There was no effect on the length of hospital stay or mortality. These results are however different from the results of a study of early compared with late parenteral nutrition supplementation in critically ill adults. In this study including 4,640 patients, the late initiation of parenteral nutrition was associated with faster recovery and fewer complications than early initiation [37]. This study is controversial and has arguably raised more questions than answers. Major problems in the study design have to be considered. It is clear that some inappropriate patients were included. Many had no nutritional deficits, and after only 3 days, more than 50% of the patients had already been discharged from the ICU. These patients are not usually considered for parenteral nutrition. In addition, the energy intake in the early initiation group was too high as judged by many current guidelines. Moreover, in the first 2 days, patients received only a 20% glucose solution with no amino acids or lipids. This is certainly not a standard form of parenteral nutrition! The claim that early initiation of parenteral nutrition is harmful is also in contrast with the results of a recently published study by Doig et al. [38], who showed that early parenteral nutrition was associated with no more complications.

Immunonutrition and Special Substrates

For two decades, attempts have been made to improve the outcome in specific patient groups using specific pharmaconutrients. The usual aim has been to lower inflammation and offset oxidative stress in patients with the systemic inflammatory response syndrome, sepsis, acute respiratory distress syndrome or acute lung injury. The substrates used (e.g. ω -3 fatty acids, glutamine and antioxidants) have been used either alone or combinations thereof. For surgery, burn and trauma patients, enteral nutrition has been productively studied in combination with arginine, ω -3 fatty acids, nucleotides, glutamine and antioxidants in order to enhance the immune response to infection.

The best evidence for this style of immunonutrition can be found with enteral nutrition in surgical patients undergoing major gastrointestinal cancer surgery. It was clearly shown that pre- or perioperative nutrition with an enteral formula including arginine, ω -3 fatty acids and nucleotides reduces complication rates and shortens the length of hospital stay irrespective of the initial nutritional status [39]. In addition, this approach was found to be cost-effective [40]. In surgical patients, it was also shown that parenteral nutrition supplemented with ω -3 fatty acids was more beneficial than standard paren-

teral nutrition. The meta-analysis from Pradelli et al. [41], which included both elective surgery and critically ill patients, demonstrated a 39% reduction in infection rates, a 2-day shorter length of stay in the ICU and a 3-day shorter stay in hospital. There was no difference in mortality. A more recent systematic review and meta-analysis included only critically ill patients [42]. Here, it was found that lipid emulsions containing ω -3 fatty acids may reduce mortality and ventilation days in the critically ill. However, because of the paucity of clinical data, there was inadequate evidence to make a firm recommendation for the routine use of ω -3-fatty acids containing parenteral feeds [42].

Until recently, glutamine supplementation was recommended for all critically ill patients. It was found that low plasma glutamine levels increase mortality and therefore it was considered logical that the supplementation of glutamine should be beneficial [43]. In patients with burns and trauma, enteral nutrition with glutamine has been reproducibly shown to be effective and this can still be recommended. The data pertaining to other conditions are less clear-cut however.

For parenteral glutamine supplementation, quite a number of positive studies have now been published, and initial systematic reviews and meta-analyses indicated beneficial effects, with reductions in infectious complications, mortality and length of hospital stay (www.criticalcarenutrition.com). However, those recommendations are now under very careful scrutiny after the recent publication of two major studies in which the former positive results could not be confirmed. In the SIGNET study from Andrews et al. [44], supplementation with glutamine showed no beneficial effects. In the REDOXS study, which included 1,203 patients, supplementation with glutamine with or without antioxidants led to a significantly higher mortality than in the groups without supplementation of glutamine or antioxidants [45]. Clearly, we have to reconsider the use of glutamine. It is quite possible that the negative results of the REDOXS study are the consequence of its design. An unusually high dose of enteral and parenteral glutamine (enteral 30 g and parenteral 0.35 g per kilogram BW per day) was given. This generous provision of glutamine was maintained even when feeding was minimal. Furthermore, severely ill ICU patients with failure of two or more organs, and a high proportion of patients with renal failure were included. Previously, these very sick patients with renal failure have generally not been treated with glutamine and certainly not with such high amounts. Accordingly, the real benefit or harm of glutamine is at present unclear. The new findings have to be incorporated into discussions of all the published data on glutamine. There may be subgroups of patients who benefit from glutamine while others will be harmed, and the dose given (and perhaps the route) may also be crucial. The

most recent systematic review from Wischmeyer et al. [46] (which included the SIGNET study but not the REDOXS study) found significant decreases in hospital length of stay and hospital mortality. Infectious complications were reduced only when glutamine was given enterally. Overall mortality was unchanged in patients receiving enteral and parenteral supplementation. At the moment, most experts in this field still recommend parenteral glutamine supplementation for critically ill patients needing parenteral nutrition. We recommend that the dose to be given and the contraindications for glutamine should be those established in the REDOXS study.

Conclusion

It has to be kept in mind that an impaired nutritional status affects patient outcome. Therefore, all patients should undergo a screening and assessment process to identify patients at risk. Optimal nutritional support depends on the patient's underlying disease and the severity of undernutrition. The appropriate provision of nutrients depends on the patient's condition. Oral nutrition, with or without supplements, or enteral or parenteral nutrition should be used according to the underlying problems. The adequate provision of energy and protein is essential to improve outcomes. Specific diets or nutritional formulae can have a further impact on outcome in specific situations. To determine the best nutritional support currently available, it is useful to consult the guidelines created for specific patient groups. Oral or enteral immunomodulating substrates have been shown to be beneficial in patients with major surgery. For ICU patients, the situation is no longer so clear because of the newly published data on glutamine; further evaluation of all the data is clearly needed but should lead to a more final conclusion in the near future.

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Rémy Meier: speaker engagements with honoraria for the following companies with an interest in nutrition: B. Braun (Aesculap), Nestlé, Fresenius-Kabi and Danone, and consulting with honoraria for the following companies with an interest in nutrition: Nestlé, Fresenius-Kabi and Danone.

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