Nutritional Deficiency & Impact on Health

Chapter 2

Nutritional Deficiency and Nutrition Requirements in Critically ill Patients; Clinical Nutrition Guideline for Critical Care Management

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Abstract

Nutrition support has become a standard of care in ICU treatment protocol. The knowledge of metabolic requirements is essential to define an artificial nutrition regimen. Optimum and early nutrition either by Enteral (EN) or Total Parenteral Nutrition (TPN) can improve the ICU outcome critically ill patients are unable to eat. Nutrition authorities have long recommended providing generous amounts of protein and calories to critically ill patients, either intravenously or through feeding tubes, in order to counteract the catabolic state associated with this condition. In practice, however, patients in modern intensive care units are substantially underfed. Several large randomized clinical trials were recently carried out to determine the clinical implications of this situation. Contradicting decades of physiological, clinical, and observational data, the results of these trials have been claimed to justify the current practice of systematic underfeeding in the intensive care unit. This chapter explains and suggests how to resolve and management this conundrum.

1. Introduction

The intensive care unit (ICU) patient presents a number of nutritional challenges. The case mix of patients admitted to intensive care units may range from those admitted electively after major elective surgery to those admitted as emergencies after some surgical catastrophe, major trauma, sepsis, or respiratory failure. The variation in age range and prior health status may be extreme and nowadays ICUs are admitting increasingly more elderly, frail, or malnourished patients whose nutritional reserve may be severely compromised [1].

Nutritional support in the acutely ill is a complex subject. Several recent studies have led to considerable changes in our understanding of the metabolic response to critical illness and of various aspects of nutritional management, including monitoring of the metabolic response and the determination of caloric, protein, and micronutrient requirements. The aims of this chapter are to summarize recent findings, to highlight areas of consensus and controversy, and to define priorities for nutritional intervention in ICU patients.

Catabolism combined with malnutrition can lead to several unwanted clinical sequelae:

Impaired wound healing.

Impaired immune response

Impaired coagulation capacity

Impaired gut function.

Muscle wasting

Reduced respiratory muscle function

Evidence suggests that nutrition support can slow catabolism in ICU patients. This can improve patient outcome and reduce subsequent duration of recovery, thereby leading to a reduced length of hospital stay and reduced overall hospital costs. A number of studies have shown that survival from intensive care was improved with better nutritional adequacy and with the use of evidence based nutrition support guidelines. The overall goal of feeding ICU patients is to provide nutrition support to those who need it, consistent with their medical condition, nutritional status, metabolic capability and available route of administration [2].

1.1. Recognition of prior nutritional status

Many patients admitted in emergency may have been suffering an illness and have had poor nutrition before admission to intensive care. The best assessment of prior nutritional state

is a detailed history of prior illness and nutritional intake combined with clinical examination of fat and muscle distribution. Body mass index (BMI = weight in kg/height in m^2) is useful but weight can be difficult to obtain accurately and may be distorted by resuscitative fluid administration. We know that ICU patients suffering from under-nutrition with a limited nutrition reserve have a poorer outcome1 and that having a low BMI has been shown to be an independent predictor of excess mortality in multiple organ failure [3].

1.2. Prevalence rate of malnutrition in ICU

Malnutrition is common in acutely ill patients, occurring in 30- 50% of hospitalized patients. This prevalence may be higher in critically ill patients. Hospital malnutrition has been associated with an increased risk of complications, particularly in surgical patient. Malnutrition in hospitalized patients also increases hospital costs and is associated with increased long-term mortality. Unfortunately, patients' nutritional status often becomes significantly more compromised during their ICU stay, due to a number of factors, some intrinsic to the patient and some iatrogenic. Most troubling is data showing that more than half of all ICU patients worldwide are significantly underfed based on the energy they are prescribed to receive for the first two weeks of ICU care. In addition, to nutrition's probable key role in survival in the ICU setting following an acute illness/injury, significant mortality occurs after critically ill patients are discharged from hospital. More than 50% of the 6-month mortality following severe sepsis occurs after the patient has been discharged from the ICU. Many of these deaths are believed to occur indirectly as a result of catabolism, loss of lean body mass, lack of therapeutic physical activity, and ultimately weakness and inability to walk [4]. Therefore, nutritional support plays a vital role in prevention of nutritional deficiency in the ICU patients which leads to better clinical outcome, lowers the infection rate and reduces the hospital stay.

2. Energy Requirement and Macronutrient Deficiency ICU Patients

There are a few ways of doing estimating the resting energy expenditure.

Predictive equations: One can calculate the likely resting energy expenditure using an empirically derived formula- for example, the Harris-Benedict, the Franken field, the Ireton-Jones, or the Fusco. These are obviously only guides, and the numbers they produce may be completely wrong.

Indirect Calorimetry: One can measure the energy expenditure of the whole body using the metabolic cart. This is the gold standard. Problem is, the cart tells you how much energy the organism is using, but not how much energy it needs.

Cheating: one can crudely estimate that a human organism might need about 25 kcal/kg/day. This is the so-called "ACCP standard" (after the American College of Chest Physi-

cians). The precise estimate is 25-30kcal/kg/day of actual body weight, or 21kcal/kg of ideal body weight [5].

Glucose

Glycemic control among critically-ill patients has been a topic of considerable attention for the past 15 years. An initial focus on the potentially deleterious effects of hyperglycemia led to a series of investigations regarding intensive insulin therapy strategies that targeted tight glycemic control. As knowledge accumulated, the pursuit of tight glycemic control among critically-ill patients came to be seen as counterproductive, and moderate glycemic control came to dominate as the standard practice in intensive care units. In recent years, there has been increased focus on the importance of hypoglycemic episodes, glycemic variability, and premorbid diabetic status as factors that contribute to outcomes among critically-ill patients.

The prevalence of hyperglycemia in critically ill patients is difficult to estimate because the diagnosis is variably defined. Approximately 75% of all patients, including diabetics, have blood glucose concentrations > 110 mg/dL at the time of admission, and 12% of all patients have blood glucose concentrations > 200 mg/dL. Another study showed that > 60%, 38% and 23% of patients had blood glucose concentrations > 110 mg/dL, > 150 mg/dL and > 200 mg/dL after admission in the medical ICU of a tertiary care medical center, respectively. Glucose values > 140 mg/dL occur in 51%-58% of patients presenting with acute myocardial infarctions (MIs). Latham et al found that 21% of cardiothoracic surgery patients developed postoperative blood glucose levels of > 200 mg/dL. The prevalence rates of hyperglycemia were 86.7%, 61% and 35.2% for pediatric patients with maximal glucose levels of > 110 mg/dL, > 150 mg/dL and > 200 mg/dL, respectively. Faustino et al reported prevalence data of 75%, 50.1%, and 26.3% in pediatric patients with cut-off values of 120, 150 and 200 mg/dL, respectively [6].

Hyperglycemia

Elevated blood sugar levels are commonly seen among critically ill patients, including those without a known history of diabetes. There are many reasons why patients undergoing treatment for critical illness develop hyperglycemia, and these reasons include both effects of endogenous stress responses and byproducts of medical interventions. Inflammatory cytokines and stress hormones, including cortisol and epinephrine, serve to inhibit insulin release and promote insulin resistance, thereby naturally increasing blood glucose levels by stimulating gluconeogenesis and glycogenolysis while impeding glucose uptake by peripheral tissues.

Many medical therapies further promote hyperglycemia, including the administration of exogenous catecholamines and corticosteroids, the infusion of dextrose for the purpose of suspending intravenous medications or providing parenteral nutrition, and even bedrest, which

in and of itself may serve to impair glucose uptake in skeletal muscles. Prior to the publication of the first Leuven trial, many practitioners viewed moderately severe hyperglycemia among critically ill patients to be either an epiphenomenon or an adaptive response, not warranting significant concern or intervention. However, as observational studies accumulated linking hyperglycemia to negative in-hospital patient outcomes, this permissive attitude began to change. Hyperglycemia was coming to be seen as complication worthy of physician attention. For example, a retrospective study of 1826 patients admitted to a mixed ICU in Stamford, Connecticut serving medical, surgical, and coronary patients reported reduced survival among those with elevated mean blood glucose levels, with a stepwise effect resulting in higher mortality as mean blood glucose levels rose. Compared to patients who survived to hospital discharge, those who died had higher initial (175 mg/dL vs 151 mg/dL), mean (172 mg/dL vs 138 mg/dL), and maximum (258 mg/dL vs 177 mg/dL) blood glucose levels. In-hospital mortality was 9.6% among those with a mean blood glucose of 80-99 mg/ dL, 29.4% among those with a mean blood glucose of 180-199 mg/dL, and 42.5% among those with a mean blood glucose greater than 300 mg/dL.

Observations such as these raised concern that acute hyperglycemia was itself contributing to poor outcomes, potentially by leaving affected patients susceptible to at least some of the consequences that have long been observed among chronic diabetics, including high infection rates, poor wound healing, and polyneuropathy. Laboratory studies have also raised concerns about the possible deleterious effects of acute hyperglycemia, as hyperglycemia has been shown to cause injury to a variety of cell types that exhibit insulin independent glucose uptake, including endothelial cells, hepatocytes, and renal tubular cells. The repeated observation that hyperglycemia is associated with worse outcomes among critically ill patients, together with the theoretical harms of acutely elevated blood glucose levels, represents the basis for focusing on glycemic control in the intensive care setting. However, the possibility remains that elevated blood glucose levels are actually beneficial to the critically ill individual, and that stress hyperglycemia is an appropriate and adaptive response to life-threatening illness, as no randomized trial investigating glycemic control has studied the effect of truly permissive hyperglycemia. Potential benefits of hyperglycemia in the critically ill individual include promotion of glucose delivery in the face of ischemic insults (down an enhanced glucose diffusion gradient), with insulin resistance favoring redistribution of available glucose stores toward cells of the immune and nervous systems, and away from peripheral tissues. Recent observational studies have provided some support for this view, reasserting the possibility that hyperglycemia is simply a marker of illness severity. For example, a recent retrospective study of 7925 consecutive critically ill patients admitted to three mixed ICUs in Australia showed that while hyperglycemia was associated with in-hospital mortality, once lactate levels were considered, there was no independent association between hyperglycemia and mortality. This finding was consistent with a previous retrospective study, which found that among a cohort of

septic nondiabetic adult patients, hyperglycemia noted on initial presentation did not increase mortality risk unless accompanied by concurrent hyperlactatemia. Such observations present a useful reminder that our understanding of the effects of hyperglycemia remains incomplete. Our ability to identify patients most likely to suffer harm from hyperglycemia also remains incomplete. Several studies have concluded that the association between hyperglycemia and in-hospital mortality is attenuated among those with pre-existing diabetes mellitus, with some even failing to demonstrate any association at all [7].

Hypoglycemia

As clinicians and investigators have grappled with the results of the NICE-SUGAR trial and of other negative studies regarding the use of intensive insulin therapy in critically-ill patients, several potential explanations have been proposed to account for the lack of demonstrable benefit for tight glucose control. The proposed explanations have targeted either the rationale for intensive insulin therapy (positing that hyperglycemia may be beneficial, or that exogenous insulin may be harmful), or the execution of the strategy (suggesting that the labor-intensive focus on tight glycemic control distracts from other considerations, or that the benefits of normoglycemia have been obscured by an inability to avoid hypoglycemia). This final consideration that hypoglycemic complications negate the potential benefits of tight glycemic control-has gained widespread acceptance, and has important implications for future study of glycemic management among critically-ill patients. Hypoglycemia has been a commonly-reported occurrence among the patients treated with intensive insulin therapy in major trials, and severe hypoglycemia (defined as a blood glucose level less than 40 mg/ dL) has occurred in up to 28% of these patients. It was not initially clear whether the increased rate of hypoglycemia experienced among patients treated with a tight glycemic control strategy was problematic. In the first Leuven study, severe hypoglycemia was reported to have occurred 6.6-fold more commonly among patients in the intensive insulin therapy group, but no clinically significant outcomes were associated with its occurrence in any of the patients, and the issue of hypoglycemia was not addressed in the manuscript's discussion. By the time the NICE-SUGAR trial was reported, the frequency of hypoglycemic episodes among patients treated with intensive insulin regimens had become a significant concern. It was recognized that hypoglycemia could theoretically be harmful to patients by means of a number of different mechanisms, including irreversible neuronal damage, autonomic instability, cardiac arrhythmia, and alteration of inflammatory responses. The relationship between hypoglycemia and mortality was examined in a post-hoc analysis of the NICE-SUGAR trial. For the purpose of this analysis, severe hypoglycemia was defined as a recorded blood glucose level of 40 mg/dL or less, while moderate hypoglycemia was defined as a recorded blood glucose level in the range of 41 to 70 mg/ dL. Among the 6026 patients analyzed, severe hypoglycemia occurred in 3.7% of individuals, while moderate hypoglycemia occurred in an additional 45.0%. Hypoglycemic episodes were

much more common among those patients in the intensive insulin therapy group, with this group accounting for 93.3% of severe hypoglycemia and 82.4% of moderate hypoglycemia. The occurrence of hypoglycemia was strongly associated with an increased risk of death, with moderate hypoglycemia associated with a 40% increase in adjusted mortality risk, and severe hypoglycemia associated with a doubling of this risk. While these data do not prove a causal relationship between hypoglycemia and mortality, they do support the possibility that it was the increased frequency of iatrogenic hypoglycemic episodes that accounted in some measure for the excess mortality observed among patients treated with intensive insulin therapy in the NICE-SUGAR trial. To a significant extent, a desire to avoid inducing hypoglycemia has motivated the move away from treating ICU patients with intensive insulin protocols. It should be noted that the focus on avoiding hypoglycemia leaves the door open to future reconsideration of the benefits of tight glycemic control. If the problem with intensive insulin therapy is mainly an inability to avoid hypoglycemic episodes, one can imagine that the development of better glucose monitoring technologies and glycemic control algorithms (if they allow for severe reductions in the incidence of hypoglycemia) could result in improved outcomes with a tight glycemic control strategy. In recent years, the development of continuous glucose monitoring systems has received significant attention along these lines, but the benefits of continuous glucose monitoring have not yet been established [8].

Protein

One of the hallmarks of the metabolic response to injury is catabolism (negative nitrogen balance). There is accelerated proteolysis of skeletal muscle, which provides some of the substrate for increased hepatic gluconeogenesis. Reducing the rate of hepatic gluconeogenesis with somatostatin does not decrease the rate of peripheral protein breakdown, demonstrating that the accelerated rated of hepatic glucose production is not linked to the elevated level of peripheral protein breakdown. The degree of nitrogen loss is proportional to the degree of stress, and abates as the patient convalesces. The increased protein breakdown is thought to be modulated only partly by the endocrine stress hormones, such as cortisol. Instead, other mediators such as the cytokines TNF-α, IL-1, IL-6 and interferon-γ are involved in mediating catabolic activity. It is the balance between these catabolic hormones and anabolic hormones such as insulin and insulin-like growth factors that determine the degree of catabolism. A number of metabolic pathways may be responsible for skeletal muscle proteolysis, including the lysosomal calcium-activated, ATP–ubiquitin-dependent proteolytic pathway. The liver also contributes to catabolism through the increase in clearance of α-amino nitrogen (urea). After surgery the rate of this conversion is doubled. Blockade of glucagon and cortisol secretions with a combination of etomidate, somatostatin and thoracic epidural anesthesia decreased this clearance, thus indicating roles for glucagon and possibly cortisol and afferent neural reflexes in this process.

There is conflicting data regarding skeletal muscle protein synthetic activity during stress. Some studies indicate reduced (eg 31% decrease 24 h after open cholecystectomy) skeletal muscle protein synthesis, whether saline or TPN are infused. Others claim that the net negative nitrogen balance is due to an accelerated rate of protein breakdown that is in excess of an increased protein synthetic rate. Tissues with rapidly replicating cells, such as enterocytes, immune cells and keratinocytes, exhibit reduced protein synthesis. The derangement of protein metabolism is profound. Provision of TPN after open cholecystectomy does not prevent the decline in muscle protein synthesis observed 24 h after surgery. During stress there is increased hepatic synthesis of the 'acute phase' proteins such as fibrinogen, complement, immunoglobulins and C-reactive protein. Increase in these proteins is thought to lead to increased ability to fight infection. Simultaneously, there is reduced synthesis of binding proteins, such as albumin prealbumin, and transferrin [9].

Considering the adult patient at the ICU, there is still considerable controversy as to what, how, how much and when to feed this patient. In general, the discussion has concerned the amount of energy, which for many practitioners appears to be identical to the amount of 'nutrition' needed. For energy itself, it is becoming more and more clear that targeted feeding of the patient, by measuring the actual energy expenditure of the patient, is essential to optimize patient care. Most practitioners working in the ICU will be aware that muscle wasting is present in critically ill patients. However, muscle wasting may not always be recognized as the result of a negative protein balance that may be related to the actual amount of protein that is supplied with enteral or parenteral nutrition to the patient. Admittedly, this is an oversimplification of the situation on of the situation. In clinical practice, the protein needs are obtained from national or international guidelines, rather than biomarkers obtained from the patient. The usual expression for protein requirements is in gram per kilogram body weight per day. There are no specifications concerning sex, age, BMI, severity of illness and timing during the course of disease. The ASPEN guideline does in fact discriminate in obese and nonobese patients concerning protein requirement. The actual evidence base for protein requirements in the ICU, and in fact in any other healthcare setting, is very weak. There is not a single randomized controlled trial based on different levels of protein intake and relevant outcome measurement. Historically, the nitrogen balance test has been used in healthy adults to guide us concerning the level of protein that is required for maintenance of 'structure and function'. When the diet is protein free, body protein is lost from the body and the nitrogen balance is negative. The minimum amount of protein needed is the amount of protein needed to compensate the loss of body protein. However, when this amount of protein is consumed, nitrogen balance is not achieved. This is due to an inefficient use of dietary proteins, due to an 'adaptive' increase in amino acid oxidation. Current recommendations for healthy people are based on linear regression analysis of individual nitrogen balance data with a large variation in protein intake. The well tolerated level of protein intake is 0.83 g protein/kg body weight per day. The nitrogen

balance method is not ideal, the actual measurement of nitrogen losses is not easy and application of correction factors (e.g. for nitrogen loss from skin) may not be adequate and sometimes surprisingly positive nitrogen balances in adults are observed. More importantly, we do not know whether overall zero nitrogen balance is actually related to health; it is mainly a required condition for health. Two further aspects need to be addressed: diurnal protein cycling and protein turnover. The normal diurnal variation in protein balance consists of a post absorptive period with negative protein balance and a feeding period with a positive protein balance. Both diurnal cycling and nitrogen losses decrease and increase with protein intake. The concept of the anabolic threshold is related to cycling and can be used to optimize protein intake. Diurnal protein cycling is of course part of whole body protein turnover each day, although the most critically ill are continuously fed. Body protein is in a constant state of protein turnover, with protein synthesis and protein breakdown levels estimated to be in the order of 350 g/day. Notably, this is 3.5–5 times a normal daily protein intake. A reference man of 70 kg contains 10 kg of protein, which is replaced in 28 days. This is an overall value, as all individual functional proteins are synthesized by transcription and translation in very different rates. Protein turnover ensures a certain adaptability to environmental and health threats. Some proteins contain structural mistakes that compromise protein function. The level of protein turnover or cycling that is needed for maintenance of good health is unknown.

When protein supply is suboptimal, body protein is lost from the body. This is an adaptation to starvation for survival, with lower body protein mass causing lower losses and requirement. The level of protein turnover that supports adaptability, and protects against subclinical and clinical features of malnutrition and illness, is unknown. Survival is particularly at risk in the ICU. In critically ill patients, the acute response may require redistribution of available amino acids. Acute phase proteins and immune system may benefit from muscle protein breakdown. Any misfit in amino acid mixture between protein breakdown and protein synthesis will cause an increased amino acid drain and excessive muscle wasting. In a critically ill patient, the tipping point between the acute benefit of adaptability (protein function) and long term harm (muscle wasting, weakness and decreased functionality) is currently unknown. Long-term consequences are well documented and harm to functionality, such as 6 min walk test, is only regained partly after 1 or even 5 years. The ICU contains patients with a large variation in severity of illness and stages of disease. But no specified protein requirements are available. Patients can be categorized into acute, chronic and recovery phase. Currently, the literature is mainly confused about the early acute/chronic phase, in practical terms the first week of admission to ICU. First, the patient has to be stabilized and diagnosed; nutrition is considered a secondary requirement or no requirement at all. Critically ill patients around the world have protein intakes of 60% of target for up to 12 days. Acutely after surgery, protein turnover is increased and body protein is lost. Protein lost in critically ill trauma and sepsis patients were observed to be 2 kg (16%) in 10 days for the 0.9 g/kg protein intake level but only half (8%)

at 1.2 g/kg. And, in severe trauma patients, it was 0.5 kg in 8 days at zero protein intakes and half by any investigated protein intake level. Therefore, early protein requirement should at least be considered.

The higher level of protein turnover would be expected to be in part due to increased autophagy, especially when body protein structures have been compromised by trauma, surgery or metabolic disease. Autophagy is considered a housekeeping system to remove dysfunctional and toxic protein and complete cellular structures. In a critically ill animal model, fasting versus feeding resulted in catabolism, functional autophagy, improved maintenance of cell integrity and protection of organ function. This may suggest that protein feeding inhibits protein breakdown, which hampers autophagy when it is needed most. This particularly underlines the need to understand the balance between benefit now and long-term harm. A more complete parenteral nutrition formula has been shown to normalize protein turnover by high energy and protein (1.5 g/kg) supply in gastrointestinal surgery patients. Protein breakdown increased by 60% when only glucose was supplied, while with a protein intake of 1 g/kg, it was 30%. In sepsis patients, protein synthesis was not different and protein breakdown was 160% higher than the level in healthy controls with a 1 kcal/kg.h parenteral feeding. Septic patients may have such an increase in protein breakdown that the large amount of protein needed will do little benefit while doing substantial harm to the autophagy process. To increase protein supply in order to obtain zero nitrogen balance appears unrealistic and possibly harmful. Higher than 2.0 g/kg has been advised for critically ill patients, although others have suggested trophic or low feeding or late supplemental parenteral nutrition as discussed earlier.

Up to now, protein requirements of critically ill patients are not well understood or studied, but guidelines recommending 1.2 g protein/kg per day are supported. Attempts have been made to improve nutritional care of the critically ill patient. However, most studies have been trial-and-error approaches. Our improvements in clinical practice have been shown to increase protein intake as well as outcome. However, high protein feeding may also be harmful when provided to sepsis patients too early. Therefore, the delicate balance between early and high enough to keep the muscle, and late and low enough to be safe will have to be studied in much more detail. There are no data to support a lower early protein intake; there are data to support a lower early energy intake. It is clear that protein feeding should not only improve mortality, but also reduce muscle wasting, weakness, and thereby improve long-term functionality of intensive care survivors [10].

Lipids

Various stresses, including injury, sepsis and congestive heart failure, cause alterations in lipid metabolism. Lipolysis is accelerated secondary to increased β2-adrenergic stimulation. Elevated concentrations of glucagon, TNF-α, IL-1, interferon-α and interferon-γ might also

play a role in stimulating lipolysis. Stimulation of the β2-receptors increases cyclic adenosine monophosphate concentrations, which in turn stimulates the activity of hormone-sensitive lipase. The role of the newly discovered β3-adrenergic receptor in human lipolysis is still unclear. The lipolytic response to β2- stimulation is greater in lean than in obese persons. There are regional variations in the lipolytic rate, with visceral fat cells having the greatest rate due to increased activity of β2- and β3-receptors, and reduced activity of α2- adrenergic receptors. Subcutaneous fat has reduced lipolytic activity due to increased activity of insulin receptors and α2-adrenoreceptors [11].

In nutritional support, lipids have long been exclusively considered as nutrients providing calories, essential fatty acids (FAs), and fat-soluble vitamins. More recently, their role as major biologic regulators, specifically in influencing the structure and function of cell membranes, membrane receptor activities, eicosanoid metabolism, cytokine production and interactions, and gene expression, has been increasingly recognized. Consequently, it has been widely accepted that lipids play an important role in pharmaconutritional regulation of inflammatory/immune response, thereby influencing patient outcomes.

Shortly after soybean (SO)-based emulsions [composed of 100% long-chain triglycerides (LCTs)] began to be used, suspicions emerged about a relationship between lipid emulsions and several modifications in gas exchange and pulmonary inflammation. The high proportion of linoleic acid (18:2n-6) in SO (it represents more than 50% of the provided FAs) appears to be the main factor influencing these deleterious effects. Several studies showed that these alterations did not occur in patients with normal lung function or chronic obstructive pulmonary disease but only in those presenting acute respiratory failure. It seemed that these fat emulsions induced an increase in intrapulmonary shunt with reduction of the PaO_2/FiO_2 ratio occurring at the same time as an increase in pulmonary blood pressure and vascular resistances. These adverse effects flowed from the imbalance in production of vasodilating and vasoconstricting eicosanoids induced by some vasoactive substances derived from linoleic acid metabolism. In ARDS characterized by severe abnormalities in the ventilation/perfusion ratio, LCTs can have deleterious effects on gas exchange but only when LCTs are infused rapidly and in great quantities [12]. Increased knowledge of metabolic and inflammatory/ immune-modulating properties of various FAs has led to the development of new lipid emulsions for EN and PN. Consequently, lipids are becoming an increasingly important part of the therapeutic armamentarium for treating critically ill patients. Nevertheless, the complexity of their biologic effects, the inter individual genetic differences affecting both the response to injury and therapeutic intervention, and finally the incompletely known time line of post injury inflammatory and immune responses make further research necessary. With appropriate studies, we should in the near future be able to choose specific lipids for individual patients, for specific clinical situations, and at the right time to improve clinical outcome.

Overall, lipids, in particular n-3 fatty acids, emerge as powerful nutrients with pharmacologic properties potentially improving prognosis in critically ill patients. However, heterogeneity in study design makes the interpretation of available studies difficult. Consequently, larger prospective, randomized, double-blind trials with comparable methodologies are necessary for detailed evaluation of the pharmacologic impact of lipids. In addition, a better knowledge of the influence of genotypic variation and post-injury inflammatory/immune temporal patterns may improve our current therapeutic use of various fatty acids.

3. Role of Specialist of Nutrition in Nutritional Status in ICU patients

The clinical nutrition doctors is considered central to the provision of nutrition support to those patients in need of it, and is ideally placed to provide nutritional screening and assessment. Dedicated dietetic staffing to ICU has been associated with better provision of nutrition support and may result in improved patient outcomes. A recent international multicenter prospective observational study outlined best achievable nutrition practices in participating ICUs relative to evidence based critical care nutrition clinical practice guidelines. Analysis of the data showed that the presence or absence of a dietitian in intensive care had a significant effect on determining performance with respect to nutrition practices. The presence of a dietitian was associated with top performance, and was considered a primary enabling factor that affected adherence to internationally recognized nutrition guidelines in ICU. Another recent study showed improvements in early introduction and route of feeding, as well as better achievement of nutritional targets associated with the presence of an ICU clinical nutritionists [13].

4. Assessments

Nutritional Screening

All ICU admissions, should be screened to assess their need for nutrition support. Recommend nutrition support within 24 to 48 hours of ICU admission (or once hemodynamically stable) for:

Undernourished or hyper catabolic patients .

Ill patients expected to stay in ICU for 3 days or more.

Patients not expected to commence diet within next 5 days or more.

A 'nutrition risk in the critically ill score' (NUTRIC Score) has recently been validated for screening ICU patients. Further validation studies are needed [14].

Determination of Nutritional Requirements

Nutrient requirements can be calculated by over 200 different equations. Predictive

equations use traditional factors for age, sex, height, weight, and additional factors for temperature, body surface area, diagnosis, and ventilation parameters. Additional data such as injury stress, activity, medications received, and obesity have been added to improve accuracy. Several predictive equations were developed with a focus on specific patient populations and medical conditions. Predictive equations have varying degrees of accuracy. Error rates can be significant and result in under and overestimation of caloric needs that impact outcomes. Some equations are unsuitable for use in critically ill patients, while others have been validated with improved accuracy. Due to the extreme metabolic changes that can occur during critical illness, energy needs should be measured using indirect calorimetry (IC) in patients not responding to nutritional support, have complex medical conditions, and are ventilator dependent. Indirect calorimetry relies on accurate determination of oxygen consumption (VO2) and carbon dioxide production (VCO2) using precise measurements of inspired and expired fractions of oxygen and carbon dioxide. The abbreviated Weir equation uses the measured VO2 and VCO2 to determine resting energy expenditure (REE). The respiratory quotient (RQ), the ratio of VCO2 to VO2, can then be calculated. The RQ was once thought to be a means to determine nutritional substrate use, but this assumption has never been substantiated and use of the RQ measurement is of limited clinical value. Measured values of RQ between the physiologic ranges of 0.67–1.3 should be used as a way to validate test quality. Values of RQ outside of this range invalidate the results due to technical measurement errors and should be repeated.

Clinical Practice Recommendations

According to the ASPEN and ESPEN guidelines Nutritional support should be initiated early within the first 24–48 hours in critically ill patients.

Primary goals of nutritional support and care are to: preserve and maintain lean muscle mass; provide continuous assessment, reassessment, and modification to optimize outcome; monitor the patient for tolerance and complications such as refeeding syndrome; prevent protein energy malnutrition by giving higher protein content while providing adequate total calories; monitor nutrition goals and target achievement rate of > 50% within the first week; and prevent accumulation of a caloric deficit.

Indirect calorimetry should be used when available or when predictive equations are known to be inaccurate.

• Current EN practice recommendations are to: preferentially feed via the enteral route; initiate EN within 24–48 hours; reduce interruptions of EN for nursing care and bedside procedures to prevent underfeeding; maintain head of bed (HOB) elevation to reduce aspiration risk; accept GRV up to 500 mL before reducing or stopping EN in the absence of clear signs of intolerance; use motility agents to improve tolerance and reduce GRV; and promote post-pyloric feeding tube placement when feasible.

Current PN practice recommendations are to: only use PN when enteral route is not feasible; use PN based on the patient's nutritional risk classification for malnutrition; delay PN up to seven days if the patient is in Nutritional Risk Class I or II; initiate PN early if the patient is in Nutritional Risk Class III or IV; convert to EN as soon as tolerated to reduce the risks associated with PN.

Use of trophic or "trickle feeding" and permissive underfeeding may be beneficial. •

Use of pharmaco-nutrients and immune-nutrition: omega-3 fatty acids (fish oils) may be beneficial in acute respiratory distress syndrome (ARDS) patients; utilize high omega-3 fatty acid to omega-6 fatty acid ratios. The use of arginine, glutamine, nucleotides, antioxidants, and probiotics may be beneficial in specific patients. The use of arginine should be avoided in patients with severe sepsis.

Appropriate nutritional support in hospitalized patients and the prevention of malnutrition can improve outcomes and reduce health care costs. The nutritional care plan should utilize the team approach and be supported by organizational standards with policies and procedures that are based on the best available evidence. The health care team's proper implementation, continuous assessment, and monitoring of the nutrition care plan are key elements for success.

Requirements:

Before initiation of feeding, nutritional assessment should consider:

Recent weight loss

Nutrient intake prior to admission

Level of disease severity

Co-morbid conditions

Function of gastrointestinal tract

In the critical care setting, the traditional protein markers such as albumin, pre-albumin, transferrin and retinol binding protein are a reflection of the acute phase response and do not accurately represent nutritional status in the ICU setting.

Requirements should be assessed individually and provided according to tolerance. Overfeeding critically ill patients can have detrimental effects on outcome. Conversely, persistent underfeeding has been associated with increasing complications. Over aggressive feeding during the acute phase of injury may also promote adverse outcome effects [15].

Recommended macronutrient requirements are summarized in Table 1.

Table 1: Recommended macronutrient requirements for use in ICU patients.

Nutrient	Recommendation (per kg recommendations infer per kg per 24 hours.)	Guideline Source
Energy	Individualize. Use validated equations, in the absence of indirect calorimetry	PENG 2007 NSIG 2010
	Use 25-30kcal/kg, or predictive equations, or indirect calorimetry.	ASPEN 2009
	20-25kcal/kg in acute phase of critical illness. 25-30kcal/kg in recovery phase	ESPEN 2006
	25kcal/kg	ESPEN 2009
	Consider hypocaloric feeding in critically ill obese (BMI >30kg/m2), e.g. 60-70% of target energy requirements, or 11- 14kcal/kg actual body weight, or 22-25kcal/kg ideal body weight	ASPEN 2009
Glucose	3-5 (maximum 7) g/kg.	ESPEN 2006
Protein	1.3-1.5g protein/kg	ESPEN 2009
	1.2-2.0g protein/kg if BMI<30 kg/m2 2g/kg ideal weight if BMI 30-40kg/m2 2.5g/kg ideal weight if BMI >40kg/m2	ASPEN 2009
Fat/lipid	0.7-1.5g/kg	ESPEN 2006
	0.8-1g/kg in sepsis/SIRS	PENG 2007

5. Micronutrients Requirements in ICU Patients

Although great care is taken to provide adequate and optimal doses of micronutrient combinations; the essential role of micronutrients should not be overlooked. Micronutrients are helpful in intermediaries in metabolism and also for their potential roles in cellular immunity, antioxidant activity and wound healing. Micronutrients deficiency in critically ill patients may occur as preexisting condition in patient with poor nutritional status before hospitalization or as a result of severe illness or injury itself. SIRS is associated with redistribution of vitamins and trace elements from the circulatory compartment, organs and tissues which are involved in immune cell production and protein synthesis.

ROS (reactive oxygen species) released from several cell types has been emphasized as a final common pathway of tissue injury in ICU which leads to MODS and ARDS The impact of vitamin D deficiency in ICU has not been studied properly till date but recent studies documented Vitamin D deficiency with acute life threatening hypocalcaemia, cardiac failure and increased mortality in critical ill patients. Vitamin D deficiency in ICU patient may be as high as 50% with undetectable levels of Vitamin D seen in 17%. CoenzymeQ 10 levels are abnormally low in patient with septic shock but the clinical significance of this abnormality is yet to be explored [16,17].

The European critical care population is characterized by suboptimal preadmission micronutrient status: the trace elements particularly affected are selenium, iron, and zinc. Micronutrients are often overlooked during nutritional assessment and this may result in provision of suboptimal nutrition in ICU patients. Micronutrients, such as zinc, selenium, copper, and vitamins C, E, and B, are involved in various metabolic processes, either acting as catalysts or facilitating various enzymatic functions. Micronutrient deficiency can result from pre-existing malnutrition, severity of current illness, and adverse effects of therapeutic regimens or procedures. Several critical care conditions and therapies worsen this precarious status with micronutrient-containing biological losses, such as major burns, major trauma, pathological intestinal losses, and during continuous renal replacement therapy. The inflammatory response further causes a redistribution of micronutrients from the circulating compartment to organs involved in acute phase-related synthetic mechanisms. Confronted by an elevated oxidative stress, patients are not able to develop normal antioxidant and immune defenses [18,19].

Dietary supplementation with micronutrients that have physiologic effect on metabolic and immune functions have been shown to be beneficial in patients with critical illness special emphasis on selenium, zinc, Copper, Vitamin C & E. Vitamin B complex, etc. Micronutrient studies in critically ill remains few in relative term, with problems arising from a heterogeneity of patient population, large variability of patient within the same diagnostic category and absence of relevant clinical endpoints. Nevertheless, emerging evidence regarding the potential of micronutrient supplement in influencing clinical outcome in critically ill is encouraging. The sum total of available evidence still indicates that exact micronutrient requirement of the critically ill patient and related practice issues remain uncertain [20]. In **Table 2** Recommend micronutrients requirements for use in ICU patients are shown.

Table 2: Recommend some vital micronutrients requirements for use in ICU patients [21,22].

Micronutrients	RDA	Standard dose		Additional Supplementation
		PN Formula	EN Formula	
Zinc	15 mg	2.5-5 mg	11-19mg/L	10-30 mg/day
Vitamin A	1 mg	1 mg	0.9-1 mg/L	-
Vitamin C	75-90 mg	200 mg	125-250mg/L	-
Vitamin E	15 mg	10 mg	25-50mg/L	-
Vitamin K	150mcg	150mcg	40-135mcg/L	-
Selenium	50-100 mcg	20-60 mcg		100-400mcg/day
Iron	0-15 mg	0	12-20mg/L	-
Copper	900mcg	300-500mcg	-	-
Manganese	1.8-2.2 mg	60-100mcg	-	-

6. Nutrition Support Provision

6.1. Enteral nutrition

Enteral feeding is the preferred route of feeding for ICU patients.

Evidence suggests enteral feeding helps to: maintain gut integrity, prevent gut stasis, maintain gut mas. Maintain gut associated lymphoid tissue, and prevent stress ulceration. Early enteral feeding (within 24-48 hours of ICU admission) benefits ICU patients.

Enteral feeds are more nutritionally complete, are better metabolically handled, and often cost less than parenteral solutions. Standard feeds are appropriate for most ICU patients. Arginine supplemented feeds are not recommended in severely septic patients due to possible adverse effects on outcome [23].

Enteral Glutamine

Enteral supplementation of glutamine has demonstrated outcome benefits in burns and trauma patients. There are conflicting recommendations over use of enteral glutamine in other critically ill patients. Glutamine powder mixed with water can be given enterally in 2-3 divided doses to provide 0.3-0.5g glutamine per kg per day [15].

Feed administration guidelines

Closed enteral feeding systems should be used where possible.

Administration sets for closed system enteral nutrition formulas should be changed per manufacturer guidelines.

Giving sets for open systems should be changed at least every 24 hours.

Use sterile water for flushing tubes or for enteral water infusion.

Flush feeding tubes regularly. Sterile liquid formulas should be used in preference to powdered reconstituted feeds.

Closed-system enteral nutrition formulas can hang for 24 hours. Sterile decanted formulas should have a maximum 8 hour hang-time.

Reconstituted powdered feeds should have a maximum 4 hour hang-time. Store unopened liquid enteral feeds as per manufacturer's guidelines and use before expiry date.

Enteral nutrition prescriptions should include: patient identifiers, the feed formula, the enteral access device/site, and the administration method and rate. A head-of-bed elevation of 30 to 45o is recommended during feeding, unless contraindicated [24].

Feed rate guidelines

There are limited prospective data to form strong recommendations about initial starting rates for enteral feeding. Formulas are frequently commenced at full strength at a lower rate and advanced to goal rate in set increments, e.g. 20ml/hour, over set timeframes, e.g. every 8 hours, until target rate is achieved. Feeds should not be diluted (with rare exceptions). Some authors recommend commencing feeds at full target rate in stable patients. Aiming for target feed volumes per 24 hours has also been advocated to improve nutritional adequacy. 48,49 A recent ARDSNET randomized trial (EDEN trial)50 showed that early trophic enteral feeds (25% of goal calories) were associated with similar outcome benefits to full enteral feeds in younger, normo-well-nourished patients with a relatively short ICU stay. Other studies have shown that the most significant outcome benefits from full nutrition therapy occur in patients with low BMI, high BMI, and with prolonged stays in ICU (>7days). A large observational study showed that reaching >80% of nutritional target was associated with improved mortality [2,25,26].

Strategies to improve enteral feeding tolerance

For patients with inadequate feed tolerance:

Consider use of prokinetics e.g. metaclopramide and/or erythromycin, unless contrain-dicated. Efficacy declines after 2-3 days when prescribed alone, or after 6 days when pre-scribed as a combination. Routine use of prokinetics is not recommended unless signs of feed intolerance are present. Significant side-effects can occur with use of either prokinetic (seek advice from pharmacy).

Consider use of laxatives if no bowel motion, where there is no contraindication.

Reduce use of opiates where possible.

Consider patient positioning.

Ensure head of patient is elevated to 30 to 45 degrees, where possible.

Consider post-pyloric access for feeding.

Control hyperglycaemia if present.

Correct abnormal electrolytes and avoid hypokalaemia, where possible [27,28].

Disease-Specific Formulations

Immune-enhancing

One recent advance in enteral nutrition has been the use of so-called "immune-enhancing" formulas that include arginine, glutamine, nucleotides, and/or omega-3 fatty acids (fish oil) in septic and catabolic patients. A multicenter prospective randomized clinical trial with administration of such a formula (Impact; Novartis Pharmaceuticals; Basel, Switzerland) for 7 to 10 days showed reduced rates of infection and wound complications and shorter hospital stays for critically ill patients [29].

Pulmonary

Pulmonary formulas are designed to be high in fat (50%) and low in carbohydrates to reduce CO_2 production, thereby reducing ventilatory demand. In preclinical studies, a tailored pulmonary formula reduced pulmonary neutrophil accumulation and inflammatory cytokines and improved cardiopulmonary hemodynamics and gas exchange. This disease-specific pulmonary formulation contains eicosapentaenoic acid and g-linolenic acid (which modify production of proinflammatory cytokines) and antioxidants (vitamin E, vitamin C, and beta-carotene), and is a calorically dense formula, suitable in particular for fluid-restricted patients with ARDS [30].

Hepatic

Hepatic enteral formulas contain relative large amounts of the BCAAs valine, leucine, and isoleucine, with low quantities of aromatic amino acids. These products are tailored for patients with hepatic encephalopathy. The rationale is that infusion of BCAA corrects the imbalance between aromatic amino acids and BCAAs in plasma and the CNS that might contribute to the mental disturbances that are common [31]. The use of BCAA-enriched formulas for short periods may be beneficial because they improve nitrogen balance and lessen encephalopathy, but their use for longer periods becomes expensive and may limit protein synthesis, resulting in an inadequate nitrogen balance [32].

Renal

Specific renal formulas are usually low in protein or contain variable proportions of BCAA. The solutions are usually calorically dense and contain up to 2 kcal/mL. To achieve this density, some formulas may contain significant amounts of fat, the ingestion of which may result in bloating and delayed gastric emptying. Potassium, phosphorus, and magnesium are present in substantially lower amounts than is the case for typical enteral feeds. Renal patients are also at increased risk of certain micronutrient toxicities. However, it is important to feed patients adequately to avoid body cell mass catabolism and malnutrition. For critically ill patients, it is best to use dialysis to clear nitrogen and fluid and to feed them an adequate protein diet than to underfeed protein [33].

Parenteral nutrition

Consider parenteral nutrition when enteral feeding is not possible or adequate. Standard bags can be tailored to the individual by adjusting infusion rates. Daily micronutrients should be provided routinely in PN regimen or as a separate intravenous infusion. Micronutrients above the normal recommendation may be needed in case of excess loss/need. Consider parenteral glutamine [38,34].

Some authors recommend initiating PN in the critically ill if enteral feeding cannot commence within 24 to 48 hours of ICU admission. When used to supplement insufficient enteral feeding, late parenteral nutrition (day 8) was associated with improved outcomes compared with early PN initiation in one study. Another study found that supplemental PN on day 4 of insufficient enteral feeding, to reach 100% of nutrition needs, had significant outcome benefits. A reasonable trigger time of 72 hours for commencing PN in ICU, could be used where EN has failed or is contraindicated [35,36].

7. Conclusion

Supplementation of macro and micronutrients in critically ill patients due to their deficiency should be considered as a crucial component of ICU care. Recent methodologically sound and adequately powered randomized, controlled trials have not generated unequivocal evidence that feeding protocols targeting full-replacement nutrition early in the course of critical illness result in clinical benefits. The enteral route is preferred, although, if not available, most of these agents can be given by the parenteral route. In that case, however, dose recommendations are less clear. Attention to micronutrients is paramount both in optimizing the nutritional management of the critically ill and in the overall management of these patients. It also is essential in promoting positive outcomes and decreasing complications.

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