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# Nitrogen balance for estimating protein requirements in critically ill patients: a literature review

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## ABSTRACT

In critically ill patients, marked protein catabolism is prevalent. Protein demanding for such patients has been based on commending nitrogen balance, in most cases. Due to the stress response, critically ill patients tend to fall into a negative nitrogen balance state. Metabolic changes, particularly in elderly critically ill patients, increase the risk of the worsening nitrogen balance. Some evidence suggested optimal nitrogen balance may not indeed equalize to the best clinical outcome. On the contrary, several studies reported the available nitrogen balance data in establishing new recommendations for the protein required by critically ill patients. There is a hypothesis that adequate protein supplementation utilizing nitrogen balance could be correlated with improved results for patients in intensive care unit (ICU). Therefore, this literature review aims to deliver a brief explanation of whether nitrogen balance can be useful in documenting the effectiveness of nutritional therapy in critical illness or not.

**Keywords:** protein requirement, nitrogen balance, nutritional support, critical ill
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## INTRODUCTION

Critical illness has long been associated with hypermetabolism and increased protein catabolism.[1] Protein catabolism may contribute to a decrease in amino acids required for cell and tissue recovery, leading to undiminished metabolic dysfunction.[2] Patients can have more diseases, poorer immunities, and a lesser probability of survival with perennially exaggerated protein catabolism.[3,4] Several studies have found that protein supplementation is not dramatically helping morbidity and mortality of general seriously ill patients.[5,6] Recent reports, on the other hand, have indicated that protein balance is more sacrificing than the overall intake of calories or proteins for patients in the ICU.[7,8] Nutritional protein balance can be merely measured using nitrogen balance, estimated from protein consumption and urinary nitrogen production.[1,9] Even though optimal protein intake during critical diseases remains debatable, personalized or personalization of diet approach, individual patients may be worthy of reducing the negative protein balance. The optimum protein intake during critical illness can be deemed worthwhile.

### Effects of critically ill conditions in metabolic alteration and malnutrition

Critical illness is any situation that needs treatment at an intensive care unit, whether surgical or medical (ICU). While critical illness is frequently attributed to infections, some related clinical findings can occur in other conditions such as burn trauma or significant bleeding, neurological issues, including ischemia, pancreatitis, and post-operative conditions. This disorder should also be included in the category of critical illness. Critical illness is a state of hypercatabolic. The body's inflammatory reaction, which causes another degree of catabolic response relative to moderate starvation's adaptive catabolism, is the hallmark of critical illness. This sequence of occasions is governed by orchestrated cytokine reactions and neuroendocrine, which affect consumption of energy and induce perceptible catabolism of protein.[10] The immediate host reaction is located in the area where local infection or injury occur. The reaction is initiated by triggering vascular endothelial cell neutrophils, monocytes and macrophages. This response is assisted by a vasodilatation complementary activation mechanism that boosts permeability of capillary. It is relegated to interstitial fluid, and chemo-attractants are redeemed at the local injury location. In addition, specific cytokines, including interleukin (IL-1, IL-2, IL-6, the necrosis factor of the tumor (TNF), interferons, and other proinflammatory cell cytokines, are encouraged to reply to this issue. This reaction is encouraged by the addition of specific cytokines, including interleukin (IL)-1, IL-2, IL-6.[11] The cytokines are untied, and the typical symptoms and signs that respond to systems inflammation are determined at a high level after their accumulation is completed.

Increased metabolic demand for

essential diseases can contribute to lean body mass break-up that contributes to malnutrition.[12,13] Malnutrition is a chronic, sub-acute or acutes nutritional condition which has affected the composition of the body and diminished function to differing extent with or without excess surplus or undernutrition.[14] The American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics in 2012 issued a consensus that describe malnutrition as the phenomenon of two or more characteristic features: deficit of energy intake, weight, muscle mass, or subcutaneous fat, localised or widespread accumulation of body fluids and reduced functionality.[15] A consensus-based system consisting of phenotypic criteria and etiological criteria for addressing testing and evaluating malnutrition was developed in 2016 by the Global Leadership Initiative on Malnutrition (GLIM).[16] GLIM advises that a combination of at least one phenotype criteria and one etiological criterion is needed to satisfy specifications for standardization of clinical malnutrition practice (Table 1).[16]

Around one third of patients in developing countries who are hospitalised have a degree of malnutrition on entry.[13] It is predicted that the percentage of patients in two-thirds might drop more without a suitable diet treatment.[12,13] As such, nearly one third of those admitted to the hospital without malnutrition was exposed to malnutrition whilst in the hospital. In critically ill patients, malnutrition is a wide variety and a frequency ranging from 38% to 78%.[17] Malnutrition exacerbates the symptoms of such malnourished populations as well as the elevated occurrence. For example, a research revealed the independent risk factor of nosocomial infections (HAIs) in hospitalized patients was malnutrition. The responsibility of HAIs rests with patients with higher risk and sicker admission and mortality for ICU.[17] Thus, it is technically possible to detect and control malnutrition during hospital admission.

Recent data suggest that malnutrition can also impact readmission rates in hospitals.[18,19] The most critical studies, a retrospective analysis from the observation more than 10,000 sequent admissions, showed the re-entry rate in 30-day was 17 percent.[18] Comorbidity, which dramatically increased the risk of readmissions, included loss of weight (grade not defined) and iron-deficiency anemia. The results from many previous studies have demonstrated that malnutrition could impact hospital readmittance rates. Weight loss is linked to a 26% increase in readmission risk.[18,19] Evidence indicates that pre-existing malnutrition impacts post-discharge effects, including death, readmittance, and discharge to recovery centers rather than home.[13] Ultimately, early identification of malnutrition has been shown and dietary therapies in patients with malnutrition will minimize symptoms, duration of hospital stay, and readmittance rates, reducing total treatment costs.[12]

Appropriate dietary support care at the present level can be critical for optimizing outcomes.[5,10] Ultimately, diet plays a vital role in regulating inflammatory response, immune function, sluggish muscle-skeletal catabolism, tissue recovery, gastrointestinal, and pulmonary mucosal barrier maintenance.[10,11]

## Effect of hyper-catabolism on protein intake and nitrogen balance

Protein is the primary source of an energy substrate during the phase of catabolic stress in critical illness. There are no "reserve protein storage facilities" in the human body because all protein in the body is functional or structural. While the protein is used in fuel or other metabolic pathways, the protein in the skeletal muscle, connective tissue, and gastrointestinal tract is extracted through catabolism of 'labile' amino acids.[20] The skeletal muscle protein is quickly metabolized to satisfy increasing demands for injury or acute inflammatory conditions. Net protein catabolism contributes to a reduction of lean body mass as the process progresses and may contribute to organ failure and unfavourable outcomes. Protein degradation induces accelerated nitrogen excretion from the body for gluconeogenesis. The "stick of the nitrogen balance," which is the nitrogen consumption in protein minus the amount of nitrogen released, is a way to track the extent of the protein deficiency. Approximately 6.5 g of protein contains 1 g of nitrogen. In critical illnesses, net negative nitrogen balance is still present in patients, which means the excess nitrogen excretion exceeds their nitrogen intake.[21] Even though the primary condition has been resolved, they remain in the general net-negative nitrogen balance for different times. In some instances, this may take several months, such as for patients with burns. Muscular amino acids are targeted at the liver, which induces ureagenesis and raises a ammonia, uric acid, and creatinine synthesis.[20,21]

**Table 1. Phenotypic and etiologic criteria for the diagnosis of malnutrition**

| Phenotypic Criteria | | | Etiologic Criteria | |
|---|---|---|---|---|
| **Weight loss (%)** | **Low body mass index (kg/m²)** | **Reduced muscle mass** | **Reduced food intake or assimilation** | **Inflammation** |
| >5% within the past 6 months, or >10% beyond 6 months | <20 if < 70 years, or<br><22 if >70 years<br>Asia:<br><18.5 if < 70 years, or <20 if >70 years | Reduced by validated body composition measuring techniques | ≤50% of ER > 1 week, or any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption | Acute disease/injury or chronic disease-related |

GI=gastro-intestinal, ER=energy requirements.

The enhanced amino acid peripheral source effluence offers an enhanced liver gluconeogenesis buffer and a positive acute-phase synthesis of protein, which includes haptoglobin and C-reactive protein.[22] The development of negatively affecting proteins of acute-phase, such as serum albumin and prealbumin, is declining. It is also referred to as hepatic reprioritization. The complementation of ample amino acids during this process can play a significant role. It does not inhibit catabolism entirely but does allow the machinery host to fight any exaggerated protein catabolism by increasing protein synthesis. Studies have demonstrated that there is a better chance of patients having sufficient amino acid help.[20-22]

## The impact of nutrition support on critically ill patients

While it is well established that nutritional support is of potential significance to critically ill patients, evidence indicates that nutrition intervention is of considerable significance to maximize outcomes. The limited studies available about nutrition support therapies and critically ill patients' clinical effects are inconsistent and sometimes unconvincing. That is for a variety of reasons. First, nutritional intervention research numbers are often inadequate to indicate a mortality impact or other clinical effects. The experiments (for example, have a sufficient sample size) are not statistically driven to prove an impact if one is present. Secondly, the nutritional studies based on the proxy markers of serum, nitrogen balance and weight usually do not correspond or display a correlation of cause and effect for the enhancement of clinical outcome parameters, such as infection rates, mechanical ventilation period, hospital stay duration or ICU death. Third, regular nutrition trials of ICU patients are carried out. However, populations of ICU appear to be variegated, which may mask the lack of results on some ICU patients with a different disease condition in nutritional treatments that may be demonstrably effective in other ICU patients.[21,23]

There are other problems for which nutrition research can be challenging to view. In several trials, malnourished patients are ruled out because it seems immoral to deprive these individuals of their food. Fooding for comparatively healthy patients, though, may show no quantifiable outcome gain. Moreover, nutritional therapies (EN or PN) are mostly short, with only 5-10 days of an intervention being offered by patients. The period to show a therapeutic effect on patient results is concise. Finally, the clinical outcome would unlikely be dramatically changed by a single nutrient or intervention alone. These are just a few of the factors which complicate the research's ability to properly detect the effect of nutrition support therapy on the results of critically ill patients. In addition to diet therapy, there is a synergistic impact with several other approaches to improve conditions for critically ill people, such as punctual clinical treatment, sufficient nursing care and supportive physical therapy.[23]

A note to be emphasized that nutritional therapy is a medical intervention that can have adverse effects if not adequately controlled. One should be vigilant to ensure that calculated energy and protein requirements are taken carefully and that the possibility of negative effects is taken into consideration. For example, Braunschweig et al., in which intensive nutritional intervention had already been tested in patients of acute lung injury (ALI), discontinued earlier due to considerably higher interventional group deaths.[24] The authors observed that the main difference between treatments was energy supply classes and assumed that high energy distribution ($25 kcal/kg versus $17 kcal/kg) was hazardous. Energy supply should be closely monitored from all sources, and modified dietary support regime to prevent overfeeding of energy. Proper supervision is often needed to determine fluid balance, glucose modifications, insulin requirements, illnesses, patient tolerance, infections, reflux, and aspiration episodes.[23,24] The relationship between overflowing calories and increased death seems to have been noted and elaborated in several studies in review articles.[23,24] It is still unclear that the dividing line between sufficient energy supply facilitates recovery and hazardous unnecessary energy delivery. The study of Dickerson et al. found that hypocaloric (<20 kcal/kg) high protein (2 g/kg ideal body weight [IBW]) opposed to eucaloric (20 Kcal/kg), high protein enteral nutrition (EN) in critically ill obese patients resulted in shorter periods of ICU stay, decreased length, and reduced duration of enteral nutrition (EN) in patients with critical illnesses.[25] However, hypocaloric underfeeding may be helpful in some kinds of situation.[23-25]

The gold standard for energy calculation is indirect calorimetry, as no predictive equation reliably measures energy spending. In a given time, a metabolic cart is used to measure the intake of oxygen and the production of carbon dioxide and then to assess the requirements of resting energy expenditure (REE) and daily calories. Unfortunately, there are no universally accessible metabolism carts and staff qualified to run them in multiple centers. Moreover, they are hard to perform technically.[26] In comparison to energy determination, there is no clinically practical method to measure protein needs in critically ill patients. Theoretically, thus, protein requirements are measured on the basis of ideal, current or adjusted body weight measures. There are established factual protein deficiencies in critically ill patients, but the precise amount of protein required remains unclear.[20] In addition, several observer research findings have shown that sufficient protein consignment for critically ill patients is linked to shortened stay periods and lower incidence of deaths. Hypocaloric feeding while ensuring optimum protein delivery may also be an important method for certain patient populations.[5,7,13]

Energy and protein intervention will provide us with such a dilemma. Several questions are to be asked, including how to individualize protein and energy targets, what pacing, structure, and improvement in protein and energy supply during the early acute period of critical illnesses are appropriate and what optimum nutrition depends on the risk of food. Much previous research explicitly showed the value of high protein in stress situations. The results suggested that the availability of hypocaloric, slow-motion high-protein feeding could be the right option for some groups of patients. Optimization is indeed the key.

**Can nitrogen balance be useful in documenting the effectiveness of nutritional therapy?**

The protein requirement has been described as the lowest dietary protein amount to balance a person's energy balance with lack of nitrogen (N). Existent guidelines on current dietary protein intake recommendations are based on nitrogen balance studies.[27] The definition of nitrogen balance is that the discrepancy in nitrogen absorption and loss represents benefit or loss of body protein. While more nitrogen (protein) is supplied to the patient than is lost, the patient is considered to be anabolic or "positive nitrogen balance" The patient is referred to as catabolic or "non-nitrogen balance" if there is more nitrogen loss than the amount provided. Nitrogen equilibrium is generally assumed to be "nitrogen balance" between '4 or '5 g/day to +4 to +5 g/day. However, it should be remembered that the balance of nitrogen represents the net impact of nitrogen exchanges. It does not provide insight into the mechanisms of protein synthesis or catabolism or the gradual shifts in protein redistribution (for example, shifts between muscle, splanchnic tissue, and other organ systems). Evidence shows that the standard protein consumption of healthy individuals in patients with critical illnesses is insufficient.[9,25] Therefore, all existing recommendations require greater protein intake in those patients with critical illnesses, ranging from 1.2–2.0 g/kg/day to 0.80 g/kg/day for healthy patients. Still, these guidelines are however focused on inadequate evidence.

The assessment of nitrogen equilibrium has its drawbacks from a realistic point of view. Accurate identification of the intake of proteins and precise accounting of all nitrogen sources are needed for the nitrogen balance analysis. The most common nitrogen equilibrium calculation approach in clinical practice is based on the premise that a total nitrogen loss equals an additional 4g/day loss of urinary urea nitrogen.[28] The constant factor of 4 g/day indicates that 2 g loss of nitrogen is due to an extra urinary urea-nitrogen loss, as most hospitals will calculate only urea nitrogen and not the total urinary nitrogen. The other 2 g of loss out of 4 g is attributed to integumentary, gastrointestinal, and insensible damage. However, these predictions misrepresent urinary nitrogen non-urea (for example, ammonia, creatinine, uric acid, amino acids) in catabolic critically ill patients, gastrointestinal impairment in patients with diarrhea, and integumentary damage in patients with thermal injuries.[9,29] Other experiments conducted where 24-hour nitrogen balances are used as endpoints have been suggested > 2.0 g/kg/day protein.[30] However, protein levels of > 1.2 g/kg a day did not increase the nitrogen balance in randomized studies and did not affect patient-centered conditions.[31,32]

Finally, it is unclear that the stable balance of nitrogen of most critically ill patients will be determined due to interruptions in the availability of enteral nutrients and day-to-day changes in patients' clinical conditions. As other experiments have demonstrated, nitrogen equilibrium may not be an optimal representation to titrate the dose in quantity or time.[7,33] Bringing these constraints together, the losses of nitrogen and protein needs can inevitably be underestimated. Due to the absence of large randomized prospective research investigating the use of nitrogen balance through balanced-protein diets of clinical findings for critically ill patients, the justification the use of nitrogen balance as a predictor for sufficient protein intake can be challenged. Few data, however, from observational trials indicates that an increased level of nitrogen balance can benefit critically ill patients by raising protein intake above normal maintenance requirements. In a future retrospective cohort analysis, the average protein consumption of 1.5 g/kg/day versus 1.1 g/kg /day or 0.8 g/kg/day in 113 patients who were seriously ill from the operational and surgical intensive care units was significantly increased, causing enhanced mean nitrogen balance by 2.6 g/day versus <4.6 g/day versus +6.6 g/day and trending increase in intensive care unit deaths (16% *vs.* 24% and 27%, respectively).[34] In the prospective randomized study, a calorie intake designed to meet calculated or expected energy costs have been obtained in 50 critically ill patients with acute kidney injury who needed ongoing renal replacement therapy was 1.5, 2, or 2.5 g/kg/day of protein. The researchers showed that the nitrogen balance has improved by improving the consumption of proteins, and the risk of survival increased with every 1 g/day improvement on the nitrogen balance (odds ratio 1.21, p = 0.03).[35] Further study on the role of nitrogen balance in acutely ill, hospitalized patients is strongly needed in relation to clinical results.

## CONCLUSION

In critically ill patients, marked protein catabolism is generally associated. There is obviously more significant randomized research to support evidence of the nitrogen balance's therapeutic value in the estimate of protein demand for critically ill patients in the intensive care unit.

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## ETHICAL CLEARANCE

None.

## CONFLICT OF INTEREST

Authors declare that there were no conflicts of interest in this study.

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## AUTHOR CONTRIBUTION

All of the authors contributed to the study equally.

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