Nutrition Support in Critical Illness — Bridging the Evidence Gap

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The modern field of specialized nutrition support began with seminal studies showing that parenteral nutrition could stimulate growth and development in infants, as well as wound healing and convalescence in adults with the severe short bowel syndrome, who until that time had been unable to survive with enteral nutrition alone.\(^1,2\) Later, technical developments and recognition that malnutrition among hospitalized patients was common\(^3\) led to growth in nutrition support services. By the 1980s, the use of specialized regimens of enteral and parenteral nutrition were routine in intensive care units (ICUs) worldwide, despite little evidence from rigorous, controlled clinical trials supporting the efficacy of these interventions.\(^4,5\)

With time, there has been improved awareness about complications related to the use of enteral and parenteral nutrition, along with improved control of blood glucose levels and delivery of reduced caloric loads.\(^4-8\) The use of parenteral nutrition in ICUs has diminished markedly, given evidence that enteral nutrition may be generally superior for clinical outcomes.\(^6-8\) However, substantial areas of uncertainty remain (Table 1). Guidance has been based largely on expert opinion and on data from observational and small clinical trials, rather than on rigorous comparative effectiveness research.\(^6,7,9,10\) The 2009 European and American–Canadian clinical practice guidelines for ICU nutrition support differ in their recommendations for the initiation of parenteral nutrition in patients who are not expected to achieve adequate nutrient intake with enteral nutrition (oral diet or tube feedings).\(^9,10\) European guidelines suggest that parenteral nutrition be initiated within the first few days after ICU admission,\(^9\) whereas American–Canadian guidelines suggest withholding parenteral nutrition for 7 days in patients without preexisting malnutrition.\(^10\)

In this issue of the *Journal*, Casaer et al.\(^11\) describe a large (4640 patients), multicenter, randomized trial designed to address this area of uncertainty. Patients receiving early initiation of parenteral nutrition were given intravenous dextrose (20% solution) on ICU days 1 and 2; on day 2, enteral nutrition was begun (predominantly as tube feedings) with the addition of parenteral nutrition as needed to achieve the daily caloric intake goal (according to European guidelines). The late-initiation group began intravenous dextrose (5% solution) on day 1, enteral nutrition on day 2, and parenteral nutrition after day 7 as needed to achieve the caloric goal (American–Canadian guidelines).\(^6,7,10\) Nutrition support after discharge from the ICU was at the discretion of the attending physicians.

The two groups were well matched at entry according to illness severity, diagnosis, demographic characteristics, and nutrition risk scores. Mortality indexes in the two groups were similar; however, the late-initiation group had a significant (6.3%) reduction in the length of stay in the ICU and slight but significant improvements in secondary outcomes (infectious complications, indexes of organ dysfunction, and length of stay in the hospital). In addition, the late initiation of parenteral nutrition was associated with a modest reduction in total hospital costs (approximately $1,600 per patient).

Casaer et al. incorporated an upper target for blood glucose of 110 mg per deciliter (6.1 mmol per liter), which was lower than the target of...
Table 1. Major Areas of Uncertainty in the Nutritional Support of Patients in the Intensive Care Unit (ICU).*

| Clinical effect of various durations of minimal or no feeding |
| Optimal timing for the initiation and duration of therapy with enteral nutrition, parenteral nutrition alone or in combination with enteral nutrition, and micronutrients (known essential vitamins, trace elements, and minerals) in enteral and parenteral nutrition |
| Efficacy of various doses of energy, fat, and protein in enteral and parenteral nutrition |
| Effect of altered essential and nonessential amino acids (including glutamine) in parenteral nutrition |
| Efficacy of various doses and formulations of micronutrients in enteral and parenteral nutrition |
| Efficacy of alternative lipids (e.g., fish oil, olive oil, structured lipids, medium-chain triglycerides, and others, alone and in combination) in enteral and parenteral nutrition |
| Clinical efficacy of commercially available tube feedings containing combinations of antioxidants, antiinflammatory lipids, arginine, glutamine, and nucleotides in subgroups of patients |
| Efficacy of longer-term enteral or parenteral nutrition (or both) as needed in the post-ICU hospital and home setting |
| Effect of approaches for enteral and parenteral nutrition support in specific diagnostic subgroups of patients |

* Enteral nutrition includes oral complete supplements; specific oral protein, calorie, or micronutrient supplements; and complete tube feeding formulations, and parenteral nutrition refers to complete intravenous formulations.

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140 to 180 mg per deciliter (7.8 to 10.0 mmol per liter) now used in most ICUs. Patients in the two study groups had similar levels of blood glucose, so this factor did not mediate the differential responses observed. Identical and complete intravenous preparations of vitamins and trace elements were given daily to all patients, with intravenous potassium, magnesium, and phosphorus to maintain blood levels. Thus, between-group differences are probably limited to effects of the macronutrients (calories, dextrose, amino acids, and lipid emulsion) in the parenteral nutrition. Weaknesses of the study include the necessarily unblinded design and the amino acid doses, which were lower than those recommended in current clinical practice guidelines.9,10 Underlying mechanisms for the outcome differences between the early-initiation group and the late-initiation group are unclear, but differences in the length of stay in the ICU and hospital may be due to the increased rates of infection and associated organ dysfunction in the early-initiation group. The authors suggest that early initiation of parenteral nutrition may be associated with the suppression of autophagy, with inadequate clearance of damaged cells and microorganisms, but other unknown factors (e.g., altered immunity and biofilm characteristics) may also be involved.

Casaer et al. clearly show that the early initiation of parenteral nutrition to achieve caloric goals of approximately 25 to 30 kcal per kilogram of body weight per day is associated with worse clinical outcomes than those in patients in whom initiation was delayed for a week. However, these data should not be overinterpreted, since between-group differences in outcome were small, rates of death in the two groups were similar, approximately 80% of the patients were not seriously malnourished at entry (nutrition risk score, ≤4), and 60% were admitted to the ICU after cardiac surgery. Also, patients who were readmitted to the ICU and those who were seriously malnourished or were receiving established enteral or parenteral nutrition at the time of ICU admission were excluded.

In addition, patients in the late-initiation group received early enteral nutrition and daily intravenous vitamins and trace elements before starting supplemental parenteral nutrition on day 8. The optimal requirements of micronutrients for patients in the ICU are unknown (Table 1).4 Nonetheless, it may be prudent to provide complete enteral or parenteral preparations of vitamins and trace elements if parenteral nutrition is delayed in patients who cannot tolerate full enteral nutrition. Intravenous micronutrient preparations are subject to periodic market shortages; thus, consultation with health professionals and societies with experience in specialized nutrition support is important (e.g., the American Society for Parenteral and Enteral Nutrition at www.nutritioncare.org).

The findings of Casaer et al. should result in renewed attention to the nutritional needs of patients in the ICU and after their discharge from the ICU, inform the use of thoughtful nutritional care in the ICU (including the judicious use of parenteral nutrition and early use of enteral nutrition), and stimulate further study concerning the nutritional support of critically ill patients.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.