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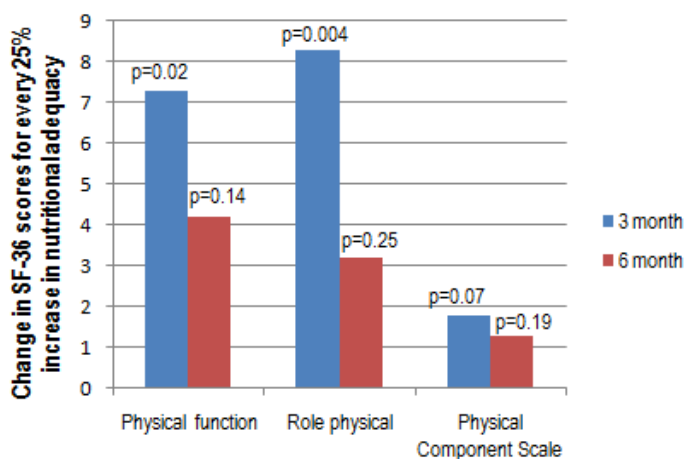
The Safety of Prolonged Use of Trophic Feeds in the Critically ill Patient: it depends on the nutrition-risk of the patient!

Over 20 years ago, User Guides to the medical literature were published in JAMA to aid readers in how to use the medical literature in making inferences about managing patients¹. To use the results of randomized clinical trials, readers were to ask themselves two important questions: 1) Are the results valid? and 2) Will the results help me in caring for my patients? In considering the answer to this last question, readers had to answer an additional question, "Were all clinically important outcomes considered?" As it relates to a recent trial of trophic feeds x 5 days vs. full feed, we ask the same question. In the original publication of the EDEN trial, investigators only reported on the short-term outcomes (ventilator-free days, ICU and hospital mortality and time to discharge, infections etc.) and observed no difference between the two groups². This led several authors or societies to recommend prolonged trophic feeding as the initial strategy in the ICU^{3,4}. We posit that it is very plausible that inadequate nutrition intake during the ICU and hospital course causally relates to the functional decline observed in surviving patients⁵ and that such recommendations to underfeed ICU patients may cause harm.

Fortunately, the EDEN investigators published a one year follow-up evaluation of survivors. Needham *et al.* reported no difference between the 2 feeding strategies in six-month and 12-month survival in 525 patients with acute lung injury⁶. These investigators reported no difference between trophic vs. full feeding in mean SF-36 PF (55 (SD: 33) vs. 55 (SD: 31), $P = 0.54$) and PCS (39 (SD: 14) vs. 40 (SD: 13), $P = 0.76$) scores at 12-months follow-up. However, they did observe a trend towards improved six minute walk tests in the full fed group – findings which were consistent with an early observation from the single center pilot study that patients in the full feed group were more likely to be discharge home without supportive assistance compared to trophic feed group¹. That is to say that there is a strong possibility that the long-term physical recovery of all ICU survivors is impaired by underfeeding during the first week ICU.

Using a large-scale observational database, we recently evaluated the association between nutritional adequacy six-month survival and health status in critically ill patients with >8 days of mechanical ventilation in the ICU⁷. We found that after adjusting for pre-selected covariates, receiving closer to target caloric prescription as early as the first week of ICU stay is associated with improved six-month survival. More importantly, receiving adequate energy in the first eight days of ICU stay is associated with improved functional aspects of health related quality of life (HROoL) among survivors of critical illness at three-month follow-up, but this association was diminished by six-months (Figure 1). From a nutrition practice perspective, the findings suggest that current recommendations to underfeed all ICU patients during the first week may be harmful to long-stay ICU patients. As a clinical community, our first mandate is to do no harm. Are we sure we are not harming surviving ICU patients by intentionally underfeeding them the first week of ICU stay?

Figure 1. Adjusted Estimated of the Effect of Nutritional Adequacy on SF-36 Scores.



Higher scores translate into greater physical function.

Not all ICU Patients are the Same!

An emerging body of evidence suggests that not all critically ill patients are the same in terms of their nutrition risk^{8,9}. The patients at high nutrition risk are more likely to benefit from nutrition therapy than others. The above observational study only focused on the 'high-risk' patients, who are those who were very sick and required prolonged mechanical ventilation. In contrast, the EDEN study recruited younger patients (average 52 vs. 62 years), had a much shorter duration of mechanical ventilation (average 5 days vs. 15 days), and the majority of EDEN patients had a body mass index (BMI) between 25-35, a range of BMI that has been shown to be unresponsive to nutritional intake¹⁰. Since it is difficult to predict who will remain in the ICU for a prolonged period, the clinical implications of these findings are that efforts to optimize nutrition delivery will be required in all patients with an understanding that the benefits may be derived only in high nutrition risk patients such as those who require prolonged mechanical ventilation or with a high or low BMI.

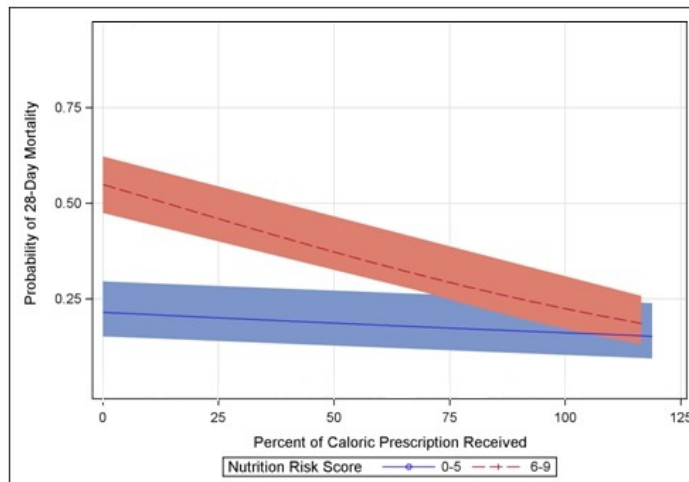
Nutrition Risk Prediction in the ICU

What these studies really speak to is the need to have better tools that will help discriminate patients that benefit the most from aggressive nutrition therapy in the ICU (or those that will not be harmed by trophic feeds for the first week). We recently developed a nutrition risk assessment tool validated specifically for the ICU patient population, the NUTRITION Risk in the Critically ill Score (NUTRIC Score)¹¹. This

score considers the age, APACHE II score, SOFA score, number of comorbidities, time in hospital prior to ICU stay and IL-6 levels and predicts for short-term mortality and duration of mechanical ventilation. Most importantly, in a subgroup of patients who stayed in ICU more than 3 days, we observed that patients with a high NUTRIC score benefit the most from aggressive provision of protein-energy requirements towards meeting their estimated requirements. On the other hand, in patients with a low score, there is no association with nutrition intake and subsequent clinical outcomes.

We recently validated the NUTRIC score in another dataset without the IL-6 levels¹². With this modified NUTRIC score, we were once again able to demonstrate that NUTRIC score predicted 28 day mortality and that increased nutritional adequacy appears to be associated with increased survival in patients with higher NUTRIC scores (not patients with lower NUTRIC scores) (Figure 2). In addition, we showed that NUTRIC score predicts for 6 month survival. In addition, since this database had 6 month survival recorded, we examined the association between NUTRIC scores and longer-term outcomes. Higher NUTRIC scores are significantly associated with higher 6-month mortality and again, there is a positive interaction between NUTRIC score, nutritional adequacy and 6-month survival. That is to say, for patients with a high NUTRIC score, increased provision of calories was associated with improved 6-month survival whereas no such relationship was observed in patients with low NUTRIC scores. One interpretation of the original NUTRIC validation study was that sicker patients tolerate less nutrition and are more likely to die from their underlying illness. In this re-validation paper, we demonstrated that nutritional intake is stable across all ranges of NUTRIC and that the relationship between NUTRIC, intake and mortality is consistent in patient with and without feeding intolerance. This argues against this explanation and suggests that in fact, NUTRIC scores are identifying patients that benefit the most from more nutritional intake.

Figure 2. Predicted Probability of Mortality versus Nutrition Received by Nutrition Risk Score



Conclusions

The NUTRIC score may be used to help determine which patients may benefit from aggressive nutrition intake during the first week in ICU (enhance EN delivery with motility agents, small bowel feeding tubes, PEP uP protocol or early supplemental PN). Future studies in critical care nutrition should recognize that not all patients are the same in terms of the benefit they receive from nutrition therapy, thus need to be more considerate of nutritional risk in their design and interpretation. It is also necessary for future clinical research evaluating outcomes of critical care nutrition to incorporate quality of life assessments. In the meantime, current recommendations advocating underfeeding in the ICU during the first week could be harming long-stay and other nutritionally high-risk ICU patients.

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