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Should we PERMIT systematic underfeeding in all ICU Patients? Integrating the results of the PERMIT study in our clinical practice guidelines.

Arabi and colleagues recently published the results of the PERMIT trial, a large-scale RCT that evaluated 2 different targets of caloric delivery to a heterogeneous ICU patient population. They randomly assigned 894 critically ill adults with a medical, surgical, or trauma admission category to permissive underfeeding (40 to 60% of calculated caloric requirements) or standard enteral feeding (70 to 100%) for up to 14 days while maintaining a similar protein intake in the two groups. The primary outcome was 90-day mortality.¹ They observed no difference in their primary outcome nor any of the other key secondary outcomes (infection, ICU and Hospital Length of stay, among others). Does this study mean that current practices of permissive underfeeding, which are rampant around the world, are acceptable and no efforts to improve nutrition delivery are warranted? To answer this question, let's consider the following points:

1) Who were these patients studied in the PERMIT study?

Similar to the EDEN trial (another large scale trial that was not able to demonstrate value to extra calories and protein²), a select number of patients who were mostly medical, young (mean age 51 years) and well-nourished (mean BMI 29.3) were recruited. We have previously shown that these patients may be insensitive to different amounts of macronutrients, particularly when looking at mortality or other short-term endpoints.³ **It is plausible that nutrition high risk patients (not well represented in this study) could still benefit from optimal nutritional delivery.**⁴

2) What was the intervention?

Notwithstanding the different caloric targets in the groups, caloric intake was low in the underfeeding and full feeding groups, both representing underfeeding (46% vs. 71%, respectively). Moreover, the protein intake achieved (mean 0.7 g/kg/day in both groups) was far below the recommended intake of 1.2-1.5 g/kg/day and only about 68% of what was prescribed in the trial. Our recent analysis suggests that optimal patient outcomes are only achieved when patients receive at least 80% of that which they are prescribed and that achieving adequate protein intake is more important than achieving adequate caloric intake.⁵ In this analysis, Nicolo et al completed a retrospective analysis on 2824 patients with a length of stay (LOS) ≥ 4 days and 1584 patients with a LOS ≥ 12 days from the International Nutrition Survey 2013.

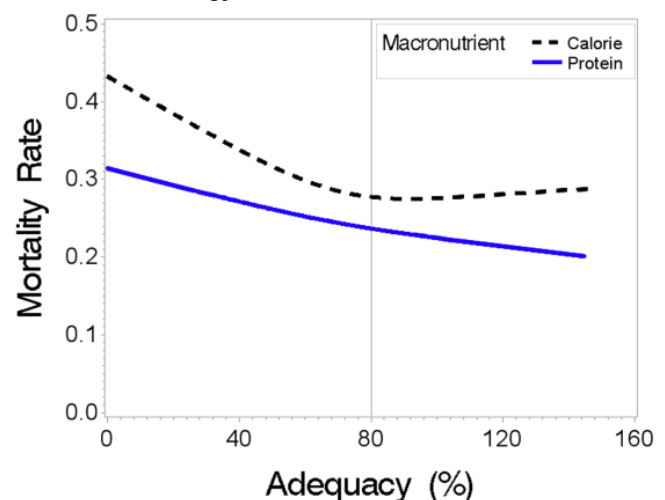
Nutritional adequacy ranged from 60-70% in both groups and achieving $\geq 80\%$ of prescribed protein was associated with reduced mortality. However, achieving $\geq 80\%$ of prescribed calories was not (see Figure 1).

It is an open question whether higher amounts of protein will translate into improved clinical outcomes for such heterogeneous critically ill patients.

3) Were all clinically important outcomes considered?

The PERMIT investigators only followed their patients for 90 days. Fortunately, the long-term follow up of patients enrolled in the EDEN study show us that the initial feeding strategy in the ICU may impact physical outcomes 1 year later.⁶ Needham et. al. observed a trend towards improved percent predicted six minute walk tests at 12 months in the full fed group compared to the trophically fed group (70% vs 63%, respectively, $p=0.136$) – 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 discharged home without supportive assistance compared to the trophic feed group.⁷ 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 in ICU. Our own recently published

Figure 1. Rate of Mortality Relative to Adequacy of Protein and Energy Intake Delivered.



observational study supports this assertion. 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 ICU.⁸ We found that after adjusting for pre-selected covariates, receiving low nutritional adequacy and moderate nutritional adequacy in as early as the first week of ICU stay versus receiving close to goal nutritional requirements is associated with a higher mortality rate at 6 months (adjusted hazard ratio (HR) 1.7, 95% Confident Interval (CI) 1.1-2.6 and adjusted HR 1.3, 95% CI 0.7-2.3, respectively). 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 (HRQoL) among survivors of critical illness at three-month follow-up where we saw improvements in function with every 25% increase in nutritional adequacy (physical function=7.3, p=0.02; role physical=8.3, p=0.004). However, this association was diminished by six-months (physical function=4.2, p=0.14; role physical=3.2, p=0.25). **So if we follow the results from the PERMIT study and continue to permit underfeeding, it is possible that we are harming some ICU patients, particularly those with long ICU stays.**

4) How generalizable are the results?

They screened over 6400 patients to enroll almost 900, so studied patients represent a select sample from the overall ICU patient population. Moreover, 70% of patients were recruited from one site in Saudi Arabia. **These factors limit the generalizability of the results to other practice setting worldwide.**

Conclusions

It is clear we need more large-scale RCTs of protein/amino acid interventions to prove that these nutritional interventions have favorably effects on clinically important outcomes, including long-term physical function. In the meantime, our first mandate is to do no harm. Given it is plausible that some ICU patients are harmed by underfeeding, we suggest that efforts to optimize both protein and calories are warranted (see Table 1 summarizing the Canadian Clinical Practice Guidelines (CPGs) recommendations on optimizing enteral nutrition (EN)).⁹

Table 1. The 2015 Canadian CPGs Recommendations on Optimizing EN

Topic Number & Title	Recommendation ⁹
2.0 Early vs Delayed EN	We recommend early enteral nutrition (within 24-48 hours following admission to ICU) in critically ill patients.
3.2 Achieving Target Dose of EN	When starting enteral nutrition in critically ill patients, strategies to optimize delivery of nutrients (starting at target rate, volume-based feeding strategies, higher threshold of gastric residual volumes, use of prokinetics, concentrated feeding solutions and small bowel feedings) should be considered.
3.3a Trophic Feeds vs Full Feeds	In patients with Acute Lung Injury, an initial strategy of trophic feeds for 5 days should not be considered.
3.3b Hypocaloric EN	Intentional underfeeding of calories (not protein) should be considered in patients at low nutrition risk. However, this recommendation does not apply to patients at high nutrition risk.

References

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